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Hemisynthesis of Some Biogenetically Anomalous 17β-Neoclerodane Diterpenoids

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Abstract

The reactivity of several natural neoclerodane diterpenoids (eriocephalin, isoeriocephalin, 7,8-didehydroeriocephalin, picropolin and picropolinone) has been investigated. The transformations catalysed by basic reagents (epimerisations at C-8, transacetylations from the C-7α to C-6α positions, formation of stable 7α,19-hemiacetals and tautomeric mixtures of 7α,19-hemiacetal and 19-hydroxy-7-keto forms) were rationalised in each case by the influence of steric and strain effects caused by the functionality and stereochemistry at the C-20 position of the neoclerodane framework. The acid catalysed nucleophilic substitution of a 20-*O*-acetyl group in 20,12-hemiacetals by a 20-*O*-methyl group was also studied. Other reactions (α-ketol rearrangements, formation of enol esters and reduction of diosphenol groups) as well as chemical correlations between several neoclerodanes were also carried out, providing useful data for the chemistry of these compounds. Finally, the hemisynthesis of teuvincentin C, starting from 6-*O*-acetylisoeriocephalin, supports our previous hypothesis on the formation of the biogenetically anomalous 17β-neoclerodane diterpenoids.

Keywords: Biomimetic reactions; epimerisation; steric and strain effects; tautomerism.

Introduction

The neoclerodane diterpenes have attracted interest in the last few years on account of their useful biological activities and challenging structures [1-4].

It is well established [5-7] that the neoclerodanes[1] are biogenetically derived from *ent*-labdanes through an 8,4-friedo backbone rearrangement, as result of that the C-17 methyl

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[1] Although the hydrocarbon skeleton of these diterpenoids is biogenetically derived from an *ent*-labdane and they should be named *ent*-clerodanes, we prefer to use the term neoclerodane proposed by Ley, S. V. and co-workers [8] because it is the nomenclature used in the majority of the articles published on this subject since 1979.

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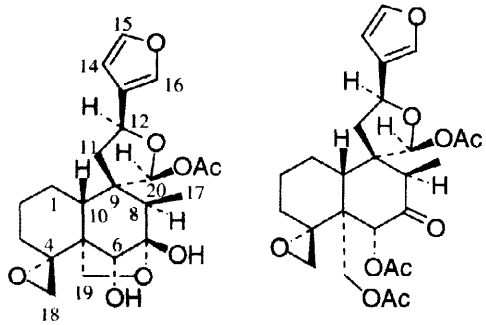
Figure 1



1 **2**

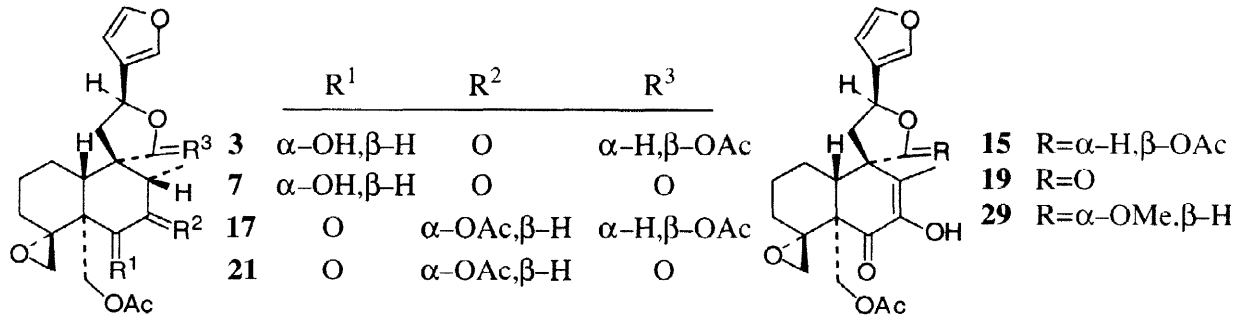
group adopts an 8α-configuration. Consequently, the vast majority of the neoclerodanes isolated from natural sources possess the C-17 methyl group in an α-configuration, and among the few exceptions reported with the opposite stereochemistry [9-12] we have recently amended [13] the structures of crotocaudin and isocrotocaudin, for which a 17β-neoclerodane framework had been claimed [10,11]. Moreover, we have suggested [12] that the well established 17β-neoclerodane structures of teuvincentin B and teuvincentin C (**1** and **2**, respectively, see Figure 1) [12] could arise from the biogenetically correct 17α-neoclerodane precursors by an epimerisation at C-8, as a consequence of the acid character of the 8β-hydrogen when C-7 bears a carbonyl function.

In this paper, we describe the preparation of some 17β-neoclerodane derivatives, including teuvincentin C (**2**), starting from suitable 7-oxo-neoclerodanes, and the results of some transformations designed to provide information concerning the driving forces that cause the epimerisation at the C-8 asymmetric centre in these compounds.

Results and discussion

Among the available natural neoclerodanes, isoeriocephalin (**3**)[14] seemed to be a suitable compound for obtaining 17β-neoclerodane derivatives by epimerisation at C-8. However, when **3** (Figure 2) and its acetates **4** and **5** (Scheme 1)[14] were treated with some basic reagents (Na_2CO_3, ^tBuOK and MeONa), very complex mixtures of products were always obtained, probably due to side reactions caused by the lability of the 20-*O*-acetyl 20,12-lactol of these compounds, which is unstable even under very mild acidic or basic conditions [14-16].

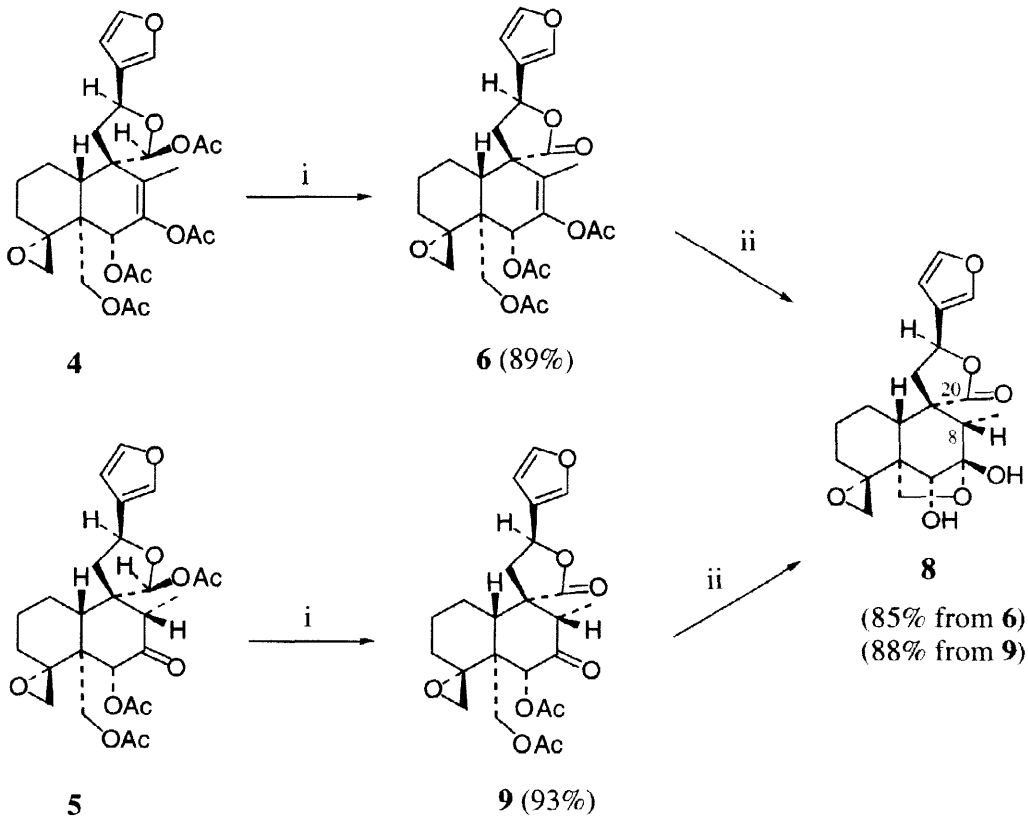
Figure 2



Oxidation of **4** with Jones' reagent (see Scheme 1) gave a compound (**6**, 89% yield) identical to the peracetyl derivative of picropolin (**7**, Figure 2)[17-20], a neoclerodane diterpene isolated for the first time from *Teucrium polium* [17]. The formation of **6** from **4**

can be rationalised by an initial acid catalysed hydrolysis of the 20-*O*-acetyl group [14,15] and subsequent oxidation of the 20,12-hemiacetal. As previously described for picropolin (**7**, Figure 2)[17], treatment of **6** with sodium carbonate in methanol solution yielded the 7α,19-hemiacetal **8** (85%, Scheme 1), which was identical to deacetylisopicropolin prepared by Brieskorn and Pfeuffer from **7** [17]. Compound **8** was also obtained in 88% yield by basic treatment of 6-*O*-acetylpicropolin (**9**)[17], which in turn was now prepared by oxidation of **5** with Jones' reagent (93% yield, Scheme 1). NOE experiments showed that **8** possessed its C-17 methyl group in an α-configuration, a structural feature not rigorously established in the previous work [17]. As shown in Table 1, the H-6β proton of **8** showed NOE correlations with the H-8β, H-10β and H_B-18 protons, as well as with both the C-6α and C-7β hydroxyl protons, thus establishing that H-6β, H-8β and H-10β protons are on the same side of the

Scheme 1



i: Jones' reagent. ii: Na_2CO_3, MeOH, reflux (2 h).

plane defined by the decalin part and, consequently, that the Me-17 group is α-oriented. Thus epimerisation at C-8 did not occur in the transformation of **6** and **9** into **8**.

Since epimerisation at C-8 of 7-oxo-neoclerodan-20,12-olide derivatives (**6** and **9**) was unsuccessful, we supposed that the 20*S*-*O*-acetyl substituent (20β-position in the formula) of **1** and **2**, which is spatially close to the Me-17 group, could be a decisive steric factor for

promoting the epimerisation, but the 20-*O*-acetyl 20,12-lactol grouping is an extremely labile function which causes undesirable side reactions (see above). For this reason, we decided to transform the 20,12-(20-*O*-acetyl)hemiacetal of **4** into the more stable 20,12-(20-*O*-methyl)acetal. It is known [12,16] that the C-20 acetoxyl group of compounds such as **4** is easily and stereoselectively substituted by alkoxide or acyloxy groups under acid catalysis, probably via an oxonium ion [16]. Treatment of a methanolic solution of **4** with catalytic amounts of toluene-4-sulfonic acid at 50 °C for 2 hours gave minor quantities of **10** (4% yield, Scheme 2) together with starting material (**4**, 70% recovered) and several decomposition products. Attempts at improving the yield of **10** by this procedure were unsuccessful. Total transformation of **4** into **10** (80% yield) and **11** (7.6%, Scheme 2) was achieved, however, when the reaction was carried out in a mixture of toluene and methanol (10:1) and traces of toluene-4-sulfonic acid under microwave irradiation for 4 minutes (see Experimental). When the microwave irradiation was continued for a further 16 minutes only

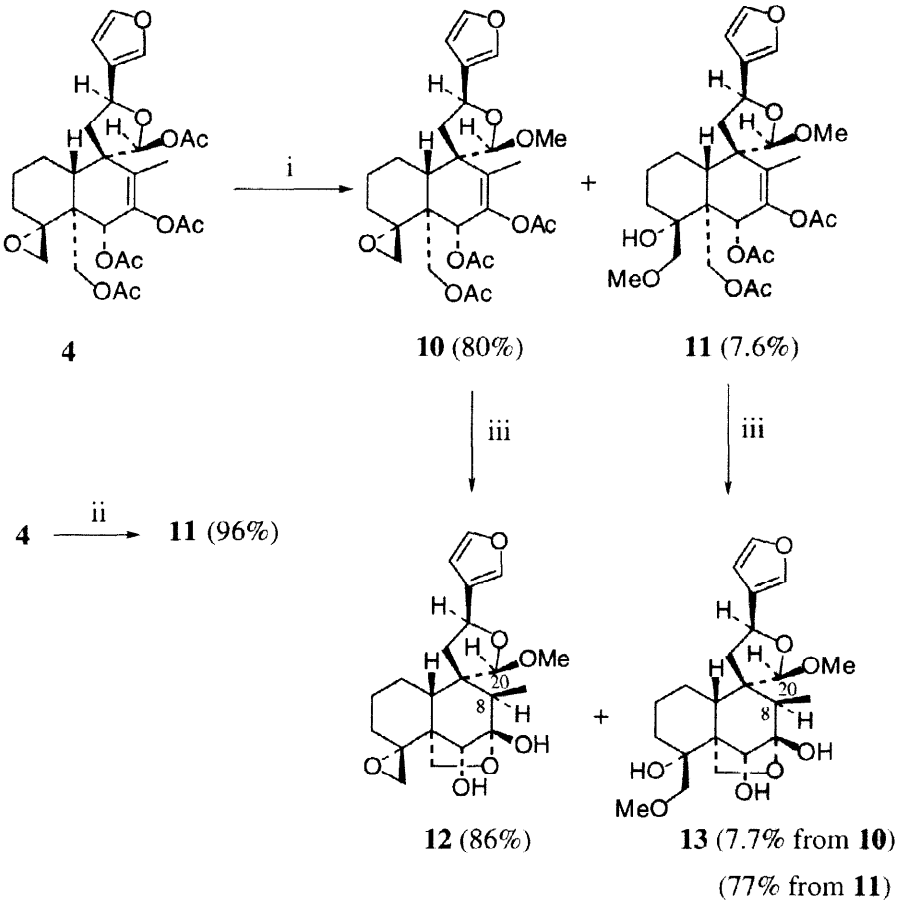
Table 1
Significant NOE data for compounds **8-10**, **12**, **25-29**, **32**, **35** and **36**[a]

Compound	Observed proton(s)	Observed NOE cross peaks with proton(s)	Configuration	
			C-8	C-20
8	H-6β	6α-OH, 7β-OH, H-8β, H-10β, H_B-18	8α-Me	-
9	H-6β	H-8β, H-10β, H_B-18	8α-Me	-
10	Me-17	20-OMe (no NOE with H-20)	-	*R*
	H-20	H_A-19, H_B-19 (no NOE with Me-17)	-	*R*
12	H-6β	6α-OH, 7β-OH, H-10β, Me-17	8β-Me	
	Me-17	H-6β, H-10β (no NOE with H-20)	8β-Me	*R*
	H-20	H-1α, H-1β, H_A-19 (no NOE with Me-17)		*R*
25	H-8β	H-7β, H-10β	8α-Me	
	Me-17	H-20		*S*
26	H-1β	H-12, H-20		*R*
	H-8β	H-7β, H-10β	8α-Me	
	H-20	H-1α, H_A-19, H_B-19		*R*
27	H-8β	H-6β, H-10β	8α-Me	
	H-10β	H-2β, H-8β	8α-Me	
	Me-17	H-20		*S*
	H-20	Me-17		*S*
28	H-6β	H-8β, H-10β, H_B-18	8α-Me	
	H-8β	H-6β, H-10β	8α-Me	
	Me-17	20-OMe (no NOE with H-20)		*R*
	H-20	H-1α, H-1β, H_A-19, H_B-19 (no NOE with Me-17)		*R*
29	H-20	Me-17	-	*S*
32	H-6β	6α-OH, H-10β, Me-17, H_B-18	8β-Me	
	H-8α	H_A-19, Me-17 (no NOE with H-6β and H-10β)	8β-Me	
	Me-17	H-6β (no NOE with H-20)	8β-Me	*R*
	H-20	H-1α, H_A-19		*R*
35	H-6β	H-7β, H-8β, H-10β, H_B-18	8α-Me	
	Me-17	H-20		*S*
36	H-6β	H-8β, H-10β, H_B-18	8α-Me	
	Me-17	H-20		*S*
	H-20	Me-17, H_B-19		*S*

[a]All these data were obtained from the NOESY spectra and, in some cases (**9**, **10**, **12**, **25-28**, **32** and **36**), also by 1D NOE experiments.

compound **11** was obtained in almost quantitative yield. As was to be expected [12,16], this reaction gave **10** through a nucleophilic substitution of the C-20 acetoxyl group by a methoxy group (**10** and **11**) and, in the case of **11**, caused an additional nucleophilic opening of the 4α,18-oxirane [21]. The 20*R* stereochemistry of **10** (and therefore of **11**) was firmly

Scheme 2



i: Toluene + MeOH (10:1), *p*-TsOH, μw (4 min). ii: Toluene + MeOH (10:1), *p*-TsOH, μw (20 min).
iii: Na_2CO_3, MeOH, reflux (3 h).

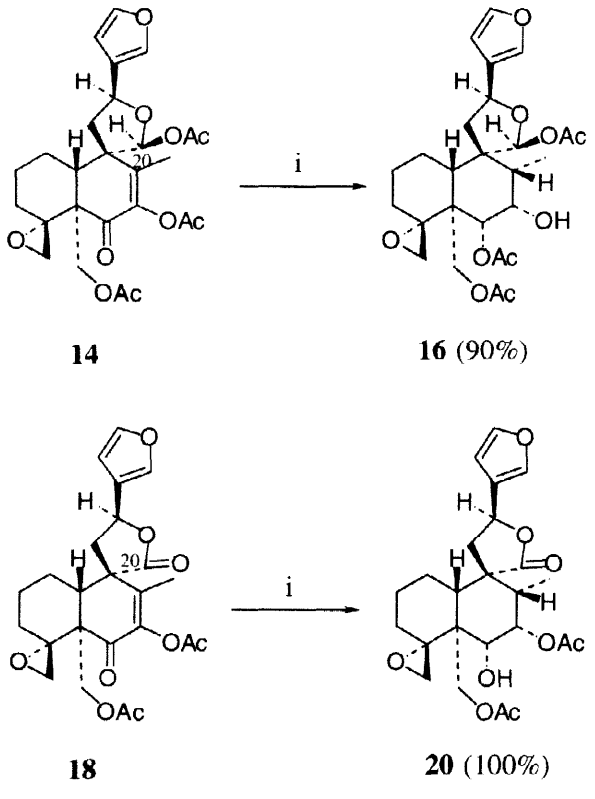
supported by NOE experiments, because irradiation at the Me-17 protons (δ 1.63) caused NOE enhancement in the signal of the 20-methoxy group (δ 3.38) and not in that of the H-20 proton, whereas irradiation at δ 5.02 (H-20 proton) produced an NOE at both the C-19 methylene protons (δ 4.60 and 4.58, see Table 1). These results established [22] that the Me-17 and 20-methoxy groups are on the same side of the plane defined by the 20,12-acetal. Therefore, the formation of **10** from **4** occurred by a stereoselective attack of the nucleophile (MeO^-) from the less hindered *si* face of the 20-oxonium ion [16].

Treatment of **10** (Scheme 2) with sodium carbonate in methanol solution gave the 7α,19-hemiacetal **12** (86% yield) and minor quantities of **13** (7.7%), whereas **11** yielded **13** (77%) by the same reaction. The C-17 methyl group of **12** and **13** is β-oriented, as was

evidenced by their spectroscopic data [12,23](see Experimental) and particularly by the NOESY spectrum of **12** (Table 1), which showed NOE correlations between the C-17 methyl group and the axial H-6β and H-10β protons.

The different behaviour of compounds **6** and **10** (Schemes 1 and 2) under basic treatment must be attributed to the presence in **10** of a bulky 20*R*-methoxy substituent, which favours the epimerisation at C-8 via an enolate anion intermediate, producing the thermodynamically more stable 17β-neoclerodane derivative **12**, in which the steric interactions between the Me-17 and 20*R*-methoxy groups are minimised.

Scheme 3



i: $NaBH_4$, MeOH-dioxane (3:1).

The influence of the functionality at C-20 on the reactivity of these neoclerodane diterpenoids was also corroborated by other chemical transformations, such as the reduction of 7-enol acetates of 6,7-dioxo compounds. When compound **14** (Scheme 3) {obtained for this work by acetylation of 6,7-didehydroeriocephalin (**15**, Figure 2)[24]} was treated with sodium borohydride it yielded **16** (90%), a compound previously known as a derivative of isoeriocephalin (**3**)[14]. This reaction caused, apart from a stereoselective reduction of the diosphenol grouping from the less hindered β face, a transacetylation reaction from the C-7α to the C-6α positions. This transacetylation can be attributed to the existence of strong steric interactions between the 20*S*-acetoxyl group (20β position in the formula) and the C-7α axial substituent. On the contrary, identical treatment of the 20,12-lactone derivative **18** (Scheme 3) {prepared for this work from picropolinone (**19**, Figure 2)[18-20]} gave **20** (quantitative yield), an already known compound [25]. In this case, the *O*-acetyl group was maintained at the C-7α position, probably due to the absence of C-20β - C-7α steric interactions.[2]

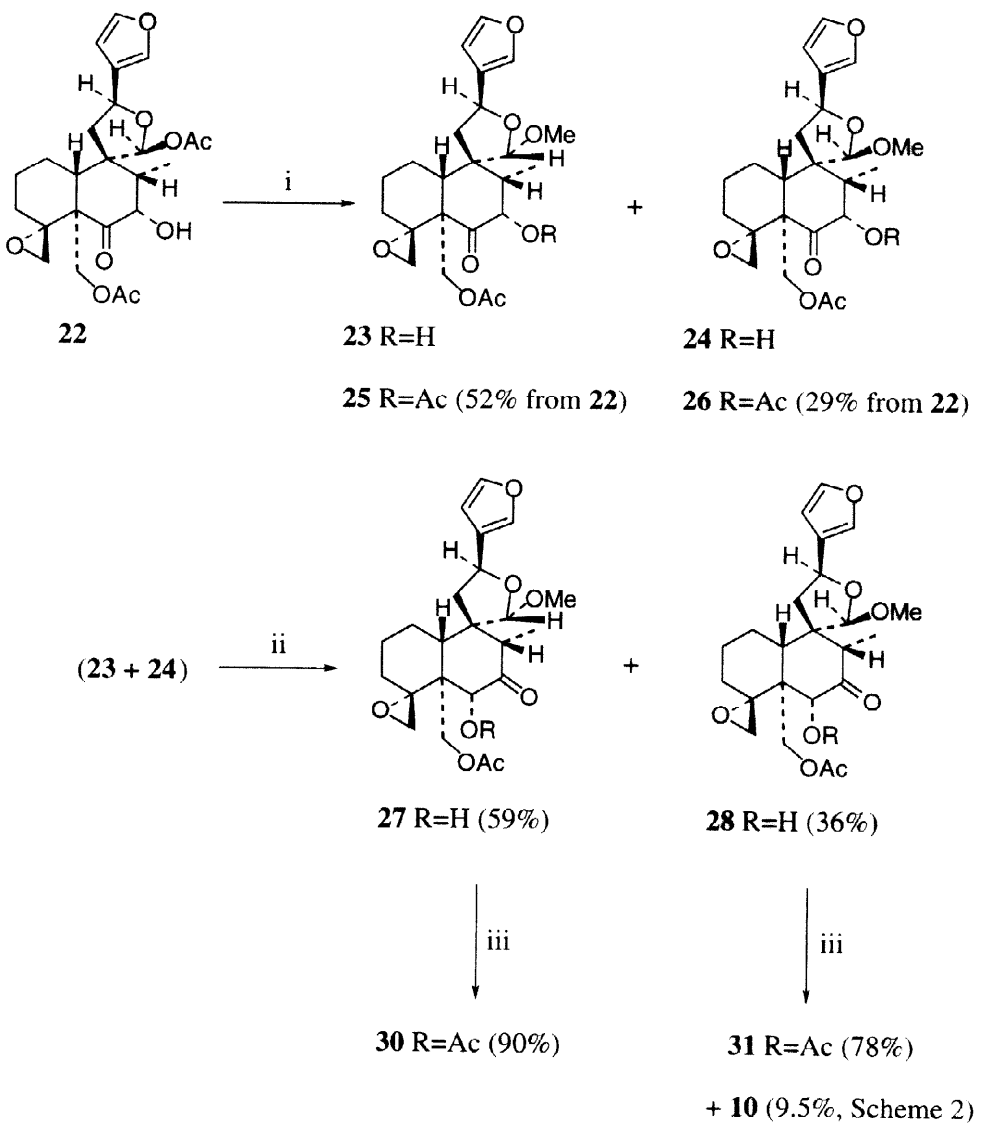
In order to provide more data on the above mentioned transformations, we decided to study the behaviour of other neoclerodane diterpenoids possessing a different arrangement of the functionalities in ring B, like eriocephalin (**22**, Scheme 4)[14,27]. Reaction of **22** (Scheme 4) with methanol and traces of toluene-4-sulfonic acid under microwave irradiation quantitatively yielded a mixture of two compounds (**23** and **24**, 2:1 ratio). Attempts at

[2] It is of interest to indicate that **14** was transformed into **5** (86% yield) by $NaBH_4$-$CeCl_3.7H_2O$ reduction, and **5** was correlated with 7-*O*-acetyleriocephalin (**17**, Figure 2)[14] by a thermal α-ketol rearrangement [26] of this last compound. Moreover, reduction of **18** with $NaBH_4$-H_3BO_3 gave **9** (84% yield), a substance previously obtained from capitatin (**21**, Figure 2)[19,20] by thermal rearrangement [26]. (See Experimental).

isolating these substances by chromatography were unsuccessful and only minor quantities of the less polar constituent (**23**) were isolated (see Experimental). Acetic anhydride-pyridine treatment of the mixture **23** and **24** gave the corresponding acetyl derivatives **25** and **26** (2:1 ratio), which were easily separated by column chromatography. Compounds **25** and **26** are epimers at the C-20 chiral centre and the NOE data shown in Table 1 rigorously established a 20*S* stereochemistry for **25** and a 20*R* configuration for **26**.

The drastic change observed in the stereoselectivity of the reaction of eriocephalin (**22**) with methanol (Scheme 4), as compared with the result achieved with peracetyl isoeriocephalin (**4**, see above and Scheme 2), may be attributed to the distorted boat conformation (^{7,10}B) of ring B in **22** [27], in which the *si* face of the 20-oxonium ion intermediate [16] is less accessible to the nucleophile attack than in **4**, thus favouring the approach of the nucleophile from the *re* face to give predominantly the 20*S* derivative **23**.

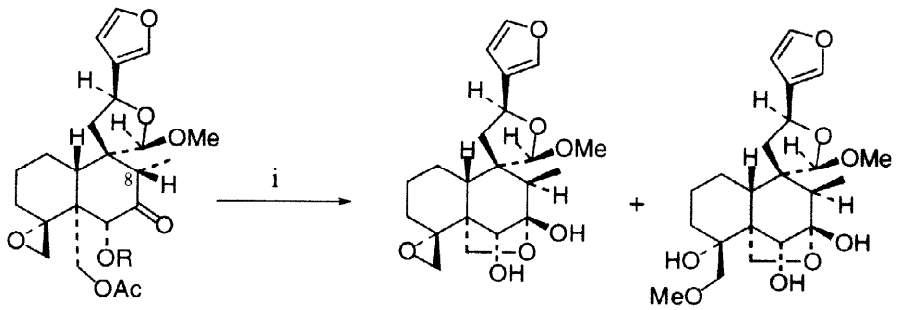
Scheme 4



i: Toluene-MeOH (5:1), *p*-TsOH, μw (6 min). ii: Silica gel, EtOAc, r.t. (55 h).
iii: Ac_2O-pyridine (1:1), r.t. (48 h).

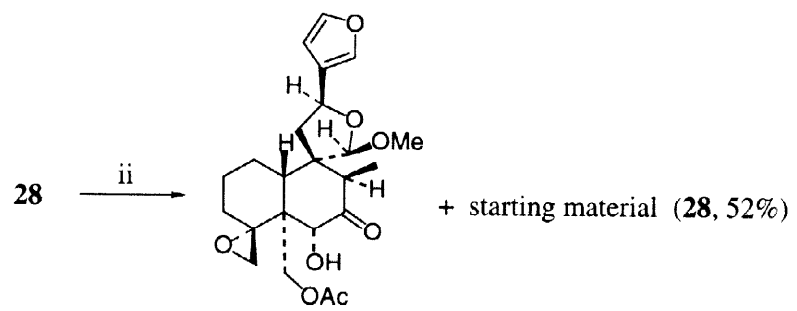
The mixture of unstable compounds **23** and **24** was almost quantitatively transformed into the corresponding stable regioisomers **27** and **28** by a silica gel catalysed α-ketol rearrangement (Scheme 4).[3] Acetylation of **27** yielded **30** (90%, Scheme 4), whereas in the case of **28** the same reaction gave the 6-*O*-acetyl derivative **31** (78% yield) and minor quantities of **10** (9.5%, Scheme 4). The different reactivity of **27** and **28** under acetylation conditions may be attributed to their opposite stereochemistry at C-20, because the formation of a 7-enol acetate (**10**) from **28** minimises the 20*R*-methoxy - Me-17 steric interactions.

Scheme 5



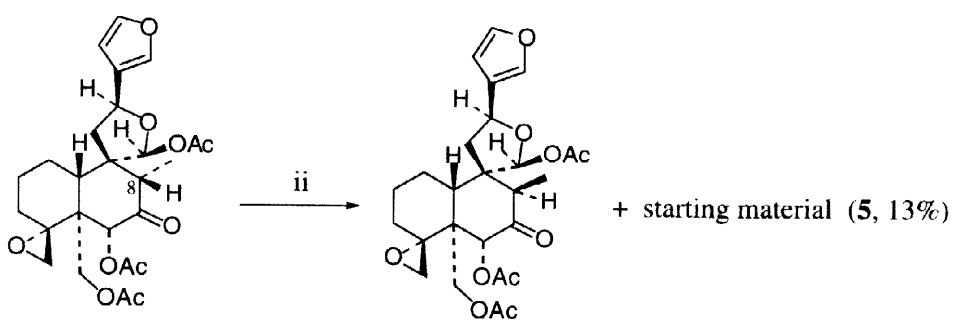
28 (R=H) or **31** (R=Ac) **12** **13**

(10:1 ratio, 92% overall yield)



+ starting material (**28**, 52%)

32 (43%)



+ starting material (**5**, 13%)

5 **2** (76%)

i: Na_2CO_3, MeOH, reflux (3 h). ii: DABCO, toluene, 120 °C (6-7 h), under Ar.

[3] It is noteworthy that reaction of isoeriocephalin (**3**) with MeOH and traces of *p*-TsOH under microwave irradiation yielded minor quantities of **27** (10%) and **28** (6%) together with several decomposition products (see Experimental). This may be due to the different conformation of ring B in **3** and **22** [14,27].

In agreement with the behaviour of **10** and **11** under basic treatment (see above, Scheme 2), reaction of **28** (or its 6-*O*-acetyl derivative **31**) with sodium carbonate in methanol solution also yielded the 17β-neoclerodane derivatives **12** and **13** (93% overall yield, Scheme 5). Similarly, treatment of **28** (Scheme 5) with 1,4-diazabicyclo[2.2.2]octane (DABCO) gave, together with starting material (52% recovered), the C-8 epimer **32** (43% yield) whose 17β-neoclerodane structure was firmly supported by its NOESY spectrum (Table 1). Additionally, when the 7-oxo-neoclerodan-20,12-olide derivatives picropolin (**7**) and its 6-acetate (**9**), as well as the 20*S*-methoxy derivative **27**, were treated with DABCO in the same conditions as those for **28** no reaction was observed.[4] Finally, reaction of 6-*O*-acetylisoeriocephalin (**5**, Scheme 5) with DABCO gave teuvincentin C (**2**, 76% yield), one of the biogenetically anomalous 17β-neoclerodane diterpenoids isolated from *Teucrium polium* subsp. *vincentinum* [12]. In the transformation of **5** into **2**, the use of DABCO as a basic catalyst prevents side reactions of the 20-*O*-acetyl 20,12-lactol grouping.

Unfortunately, it was not possible to synthesise teuvincentin B (**1**) or its 6-*O*-acetyl derivative [12] because suitable natural substrates are not available [1,2] and attempts at removing selectively the C-19 acetyl group in compounds such as **3**, **5** and **15** were unsuccessful. It is highly probable, however, that treatment of the unknown 19-deacetyl derivative of isoeriocephalin (**3**) with DABCO will produce **1**. In any case, this natural diterpenoid and the derivative **12** (see above, Schemes 2 and 5) are structurally very close.

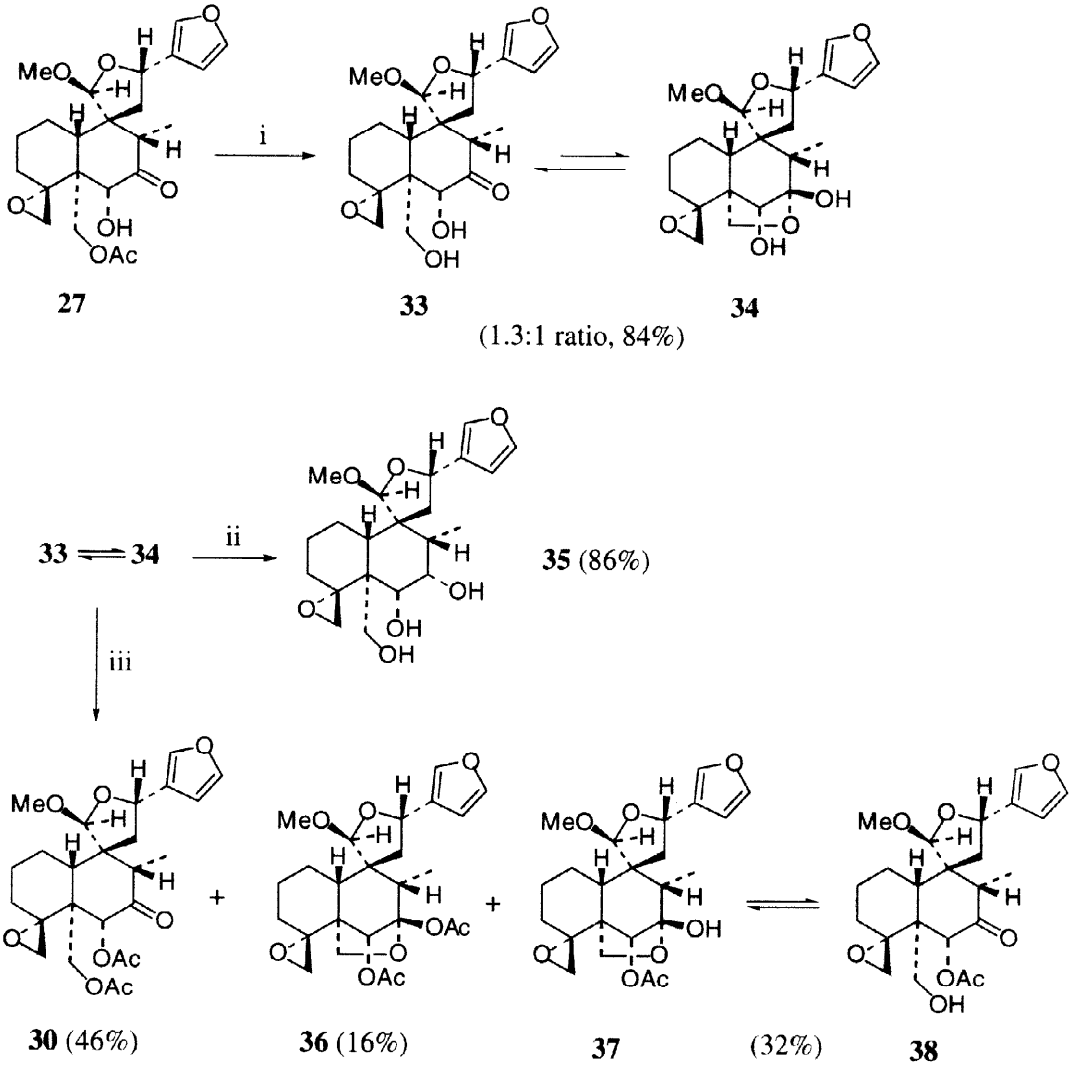
We next decided to investigate the reaction of the 20*S*-methoxy derivative **27** with a basic reagent different from DABCO. In principle, it may be expected that the steric interactions between the 20*S*-methoxy and the C-1 methylene groups in **27** could be at least of the same magnitude than those shown between the 20*R*-methoxy and Me-17 groups of **28**. For this reason, we supposed that, apart from the epimerisation at C-8 in **28** and not in **27** (see above), the behaviour of these compounds under reaction with sodium carbonate in methanol solution should be slightly different. Treatment of **27** with that reagent (Scheme 6) yielded an apparently single product, but its ^{1}H NMR spectrum revealed that it was a mixture of the tautomers **33** and **34** in 1.3:1 ratio (see Experimental). Reduction of this mixture with sodium borohydride gave **35** (86% yield), for which the NOESY spectrum (Table 1) strongly supported that, as was to be expected, no epimerisation at C-8 occurred in the initial basic treatment of **27**. Acetylation of the tautomeric mixture (**33** and **34**, Scheme 6) yielded three compounds: **30** (46%, see above and Scheme 4), **36** (16%) and another mixture of tautomers (**37** and **38**, 32%). Obviously, compound **30** originated from the 19-hydroxy-7-keto form (**33**) and **36** from the 7α,19-hemiacetal form (**34**), whereas the tautomers **37** and **38** were still found among the reaction products because of the existence of the hemiacetal form and the difficult acetylation of its tertiary hydroxyl group.[5] The NOESY spectrum of **36** (Table 1), as well as other spectroscopic data (see Experimental), rigorously supported the structure and relative stereochemistry assigned to this compound.

It is of interest to indicate that crystallisation of the mixture of tautomers **37** and **38** from EtOAc - *n*-hexane slowly yielded the 7α,19-hemiacetalic form **37**, melting point 145-

[4] When the reaction of **27** with DABCO was carried out without an Ar atmosphere minor quantities of **29** (6.3% yield, Figure 2) were obtained, probably by air oxidation or by a process in which N-oxide of DABCO takes part (see Experimental).

[5] For the conditions of acetylation of the tautomers **33** and **34**, see Experimental.

Scheme 6



i: Na_2CO_3, MeOH, r.t. (4 h). ii: $NaBH_4$, MeOH, r.t. (45 min). iii: Ac_2O-pyridine (1:1), r.t. (10 days).

147 °C. The identification of the crystalline form as **37** was supported by the following results. i) The IR spectrum of **37** (in KBr disk) showed only one carbonyl absorption at 1735 cm^{-1}, assigned to the 6α-acetoxyl group. ii) The ^1H NMR spectrum of **37** revealed that it was in equilibrium with **38** in 1:1.3 ratio ($CDCl_3$ solution at 20 °C) and this ratio changed by increasing the temperature: 1:1.5 ratio at 35 °C and 1:1.6 ratio at 45 °C (see Experimental). iii) Compound **37** showed mutarrotation from $[\alpha]_D^{19}$ -0.8° (1 minute after preparing its solution in $CHCl_3$) to $[\alpha]_D^{19}$ +22.1° (after 15 minutes). This mutarrotation from a negative value (major tautomer **37**) to a positive one (major tautomer **38**, see the ^1H NMR data quoted above) is in agreement with the fact that stable 7α,19-hemiacetal derivatives, such as **12** and **36**, possess negative specific rotations (-17.5° and -52.4°, respectively), whereas 7-oxo-neoclerodanes like **27** and **30** show positive values (+67.5° and +72.9°, respectively).

In contrast to the 7α,19-hemiacetal derivatives **8**, **12** and **13** (Schemes 1 and 2), which are stable substances in normal conditions, compounds **34** and **37** (Scheme 6) are in a tautomeric equilibrium with their 19-hydroxy-7-keto forms (**33** and **38**, respectively). The instability of these compounds must be attributed to strong steric interactions between the 20*S*-methoxy and the C-1 methylene groups, together with strain effects in the decalin moiety. In compound **36**, where the tautomerism is blocked by acetylation of the hemiacetal hydroxyl group, ring A possesses a conformation very different from those of the stable 7α,19-hemiacetals **8** and **12**, as was revealed by several ^{1}H and ^{13}C NMR spectroscopic data (see Experimental, Tables 2, 3 and 5). In particular, the proton-proton coupling values $J_{2\alpha,3\beta}$= 1.0 Hz, $J_{2\beta,3\beta}$= 8.4 Hz and $J_{3\alpha,18B}$= 0 Hz observed for **36**, as compared with those of **8** (3.3, 3.5 and 2.2 Hz, respectively) and **12** (3.3, 3.3 and 2.2 Hz, respectively), evidenced that the conformation of ring A in **36** is different from the $^{10}C_3$ chair conformation of **8** and **12**.

In summary, we have demonstrated the influence of the functionality and stereochemistry at C-20 on the reactivity of several 19-acetoxy-7-oxo-neoclerodane derivatives when they were subjected to treatment with bases. All the differences observed in epimerisation reactions at C-8, transesterification from the C-7α to the C-6α positions and in the formation and stability of 7α,19-hemiacetals may be attributed predominantly to steric and strain effects. Moreover, we have improved a method for obtaining neoclerodane-20,12-(20-*O*-methyl)acetals by a nucleophilic substitution reaction on 20,12-(20-*O*-acetyl) hemiacetals, justifiying the stereoselectivity of the reaction by the influence of steric hindrance factors. Finally, we have obtained teuvincentin C (**2**) starting from 6-*O*-acetylisoeriocephalin (**5**), thus demonstrating the validity of our hypothesis [12] on the formation of the biogenetically anomalous 17β-neoclerodane diterpenoids.

Experimental section

General experimental procedures.

Mps were determined on a Kofler-type block and are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 MC polarimeter. IR spectra (KBr disk) were obtained on a Perkin-Elmer 681 spectrophotometer. ^{1}H NMR spectra were recorded using a Bruker AM200, Varian INOVA-300 or Varian Unity-500 instrument at 200, 300 or 500 MHz, in $CDCl_3$ solution, and chemical shifts are reported with respect to residual $CHCl_3$ (δ 7.25). ^{13}C NMR spectra were recorded at 50.3 or 125.7 MHz in $CDCl_3$ and chemical shifts are reported with respect to solvent signals (δ_{CDCl_3} 77.00). ^{13}C NMR assignments were determined by DEPT pulse sequences, HMQC and, in some cases, by HMBC spectra. MS were recorded in the IE mode on a VG 12-250 instrument (70 eV, direct inlet). Elemental analyses were made with a Carlo Erba EA1108 apparatus. The purity of the compounds was checked by TLC on precoated plates (Merck, Si gel $60F_{254}$). Merck Si gel No. 7734 (70-230 mesh) deactivated with 10% H_2O, w/v, was used for column chromatography.

Starting materials, isoeriocephalin (**3**)[14], 7,8-didehydroeriocephalin (**15**)[24], picropolinone (**19**)[18-20] and eriocephalin (**22**)[14,27], were available from previous works.

Peracetylisoeriocephalin (**4**) and 6-*O*-acetylisoeriocephalin (**5**) were obtained as described previously [14].

Preparation of peracetylpicropolin (**6**) *from peracetylisoeriocephalin* (**4**).

A solution of **4** (200 mg, 0.366 mmol)[14] in Me_2CO (100 mL) at 0 °C was treated with Jones' reagent (0.3 mL) for 20 min with stirring. Then EtOH (10 mL) was added and, after a further 10 min, the reaction mixture was diluted with H_2O (200 mL) and extracted with $CHCl_3$ (4 x 50 mL). The organic extract was dried over Na_2SO_4, filtered and evaporated to dryness giving a residue from which **6** (colourless crystalline solid, 165 mg, 0.328 mmol, 89% yield) was obtained by crystallisation from MeOH. Compound **6** was identical [17] with the peracetyl derivative of picropolin (**7**)[17-20]. Since all the physical and spectroscopic data of **6** have not previously been reported [17], we include here some additional data obtained by us for this compound: mp 204-205 °C (lit. [17] mp 204 °C); $[\alpha]_D^{17}$ +58.9° (*c* 0.112, $CHCl_3$). IR (KBr) ν_{max} cm^{-1}: 3150, 1505, 870 (furan), 3045 (oxirane), 1765 (γ-lactone), 1755, 1740, 1250 (OAc), 2960, 2870, 1450, 1370, 1170, 1090, 1040, 1015, 915, 800. ^1H NMR: see Table 2. EIMS *m/z* (rel. int.): 502 $[M]^+$ (1.5), 442 (1), 340 (4), 328 (4), 312 (9), 246 (8), 218 (10), 189 (7), 159 (8), 145 (8), 135 (8), 122 (16), 94 (64), 91 (9), 81 (17), 55 (7), 43 (100).

Preparation of deacetylisopicropolin (**8**) *from peracetylpicropolin* (**6**).

To a solution of **6** (100 mg, 0.199 mmol) in MeOH (50 mL) was added Na_2CO_3 (50 mg, 0.471 mmol) and the reaction mixture was refluxed for 2 h. The reaction was allowed to reach room temperature and then acidified to pH 5 with 1N H_2SO_4. Extraction with $CHCl_3$ (3 x 25 mL) and work-up in the usual manner yielded **8** (colourless crystalline solid, 64 mg, 0.170 mmol, 85% after crystallisation from EtOAc - *n*-hexane). Compound **8** has previously been obtained from picropolin (**7**)[17] and only some physical and spectroscopic data have been reported for it. We have now obtained the following data: mp 226-229 °C (lit. [17] mp 202-205 °C, from H_2O); $[\alpha]_D^{24}$ +5.4° (*c* 0.11, $CHCl_3$). IR (KBr) ν_{max} cm^{-1}: 3480, 3380 (OH), 3150, 3110, 1500, 875 (furan), 1765 (γ-lactone), 2980, 2940, 2920, 2880, 1450, 1400, 1315, 1240, 1170, 1160, 1125, 1035, 1020, 995, 980, 925, 800. ^1H NMR: see Table 2. ^{13}C NMR: see Table 3. (Anal. Found: C, 63.89; H, 6.39%. $C_{20}H_{24}O_7$ requires: C, 63.82; H, 6.43%).

Preparation of 6-O-acetylpicropolin (**9**) *from 6-O-acetylisoeriocephalin* (**5**) *and its transformation into deacetylisopicropolin* (**8**).

Treatment of **5** (200 mg, 0.396 mmol)[14] with Jones' reagent as described above for **4** gave **9** (colourless crystalline solid, 171 mg, 0.371 mmol, 93% yield): mp 224-226 °C (EtOAc - *n*-hexane); $[\alpha]_D^{21}$ +19.3° (*c* 0.238, $CHCl_3$), identical to the previously described compound [17]: mp 221-224 °C (from $CHCl_3$-Et_2O); $[\alpha]_D^{20}$ +17.5° (*c* 0.5, $CHCl_3$); for the ^1H NMR spectrum see Table 2.

Compound **9** (120 mg, 0.260 mmol) was transformed into **8** (87 mg, 0.231 mmol, 88% yield) by treatment with Na_2CO_3 as previously described for **5**.

Preparation of (12S,20R)-6α,7,19-triacetoxy-4α,18;15,16-diepoxy-neocleroda-7,13(16),14-triene-20,12-(20-O-methyl)acetal (**10**) *and (12S,20R)-6α,7,19-triacetoxy-15,16-epoxy-4α-*

Table 2
^{1}H NMR Spectral data for compounds **6** and **8-13**[a]

H	6	8	9	10	11	12	13	J_{HH} (Hz)	6	8	9	10	11	12	13
1α	[b]	[b]	1.94 dddd	[b]	[b]	[b]	[b]	1α,1β	[b]	[b]	13.4	[b]	[b]	[b]	[b]
1β	[b]	[b]	[b]	[b]	[b]	[b]	[b]	1α,2α	[b]	3.4	4.3	[b]	[b]	3.3	[b]
2α	[b]	1.99 ddddd	[b]	[b]	[b]	1.99 ddddd	[b]	1α,2β	[b]	13.2	12.9	[b]	[b]	13.1	[b]
2β	[b]	1.49 qt	1.64 qt	[b]	[b]	1.41 m	[b]	1α,10β	[b]	12.1	12.8	[b]	[b]	[b]	[b]
3α	[b]	[b]	2.22 dddd	[b]	[b]	1.71 dddd	[b]	1β,2α	[b]	3.4	[b]	[b]	[b]	3.3	[b]
3β	[b]	1.13 dt	1.11 ddd	[b]	[b]	1.12 ddd	[b]	1β,2β	[b]	3.9	4.8	[b]	[b]	[b]	[b]
6β	5.42 br q	3.36 br s	5.17 d	5.38 br q	5.63 br q	3.68 d[c]	4.09 br s	1β,10β	[b]	4.4	3.4	[b]	[b]	[b]	[b]
8α	-	-	-	-	-	3.11 q	3.24 q	2α,2β	[b]	13.2	12.9	[b]	[b]	12.9	[b]
8β	-	1.91 q	2.56 qd	-	-	-	-	2α,3α	[b]	3.4	4.5	[b]	[b]	3.6	[b]
10β	[b]	1.92 dd	2.38 dd	[b]	[b]	[b]	[b]	2α,3β	[b]	3.3	3.8	[b]	[b]	3.3	[b]
11A	2.48 dd	2.43 dd	2.49 dd	[b]	[b]	1.91 dd	1.91 dd	2β,3α	[b]	13.2	13.6	[b]	[b]	13.2	[b]
11B	2.68 dd	2.58 dd	2.67 dd	2.44 dd	2.47 dd	2.22 dd	2.21 dd	2β,3β	[b]	3.5	4.8	[b]	[b]	3.3	[b]
12	5.50 t	5.33 br t	5.44 br t	4.91 t	4.95 t	5.01 br t	5.04 br t	3α,3β	[b]	12.9	13.6	[b]	[b]	12.8	[b]
14	6.36 dd	6.39 dd	6.36 dd	6.39 t	6.40 t	6.41 dd	6.44 dd	6β,8β	-	0	0.9	-	-	-	-
15	7.44 t	7.43 t	7.43 t	7.37[b]	7.37[b]	7.36 t	7.37 t	6β,17	1.9	0	0	1.8	1.9	0	0
16	7.45 m	7.45 m	7.45 m	7.37[b]	7.37[b]	7.34 m	7.39 m	8α,17	-	-	-	-	-	7.3	7.3
Me-17	1.51 d	1.17 d	1.13 d	1.63 d	1.64 d	1.00 d	1.07 d	8β,17	-	7.1	6.6	-	-	-	-
18A[d]	2.30 d	2.74 d	2.36 d	2.28 d	3.46 br d	2.72 d	3.73 d	11A,11B	14.3	14.0	14.4	13.9	13.9	13.5	13.4
18B[e]	3.00 dd	3.22 dd	2.92 dd	3.05 dd	3.58 d	3.22 dd	3.92 d	11A,12	8.5	9.3	9.0	[b]	[b]	8.1	8.3
19A	4.76 br d	4.14 br d	4.49 br d	4.58 br d	4.63 br d	4.14 d	4.09 d	11B,12	8.5	8.0	8.1	8.6	8.3	8.4	8.4
19B	4.84 d	4.56 d	4.42 d	4.60 d	4.98 d	4.22 d	4.80 d	14,15	1.8	1.7	1.8	1.3	1.4	1.8	1.7
20	-	-	-	5.02 s	5.11 s	4.91 s	5.04 s	14,16	0.8	0.9	0.9	1.3	1.4	0.8	0.8
6α-OH[f]	-	4.68 br s	-	-	-	3.93 d	[g]	15,16	1.8	1.7	1.8	[b]	[b]	1.8	1.7
7β-OH[f]	-	3.90 s	-	-	-	4.49 s	[g]	18A,18B	3.8	3.7	3.8	3.6	9.4	3.6	9.9
OAc	2.07 s	-	2.10 s	2.08 s	2.10 s	-	-	18B,3α	2.5	2.2	2.5	2.2	0	2.2	0
	2.05 s	-	2.04 s	2.00 s	2.03 s	-	-	19A,19B	12.8	8.3	12.9	11.7	12.3	8.3	8.4
	2.05 s	-	-	2.00 s	2.02 s	-	-	19A,6β	<0.3	<0.3	<0.3	<0.3	<0.3	0	0
18-OMe	-	-	-	-	3.32 s	-	3.41 s	6β,6-OH[f]	-	0	-	-	-	4.0	0
20-OMe	-	-	-	3.38 s	3.32 s	3.35 s	3.35 s								

[a]At 200 MHz (**6**, **10**, **11** and **13**) or 500 MHz (**8**, **9** and **12**) in $CDCl_3$ solution, except for **13** [$CDCl_3$-pyridine-d_5 (1:1)]. Chemical shifts (δ values) are reported with respect to the signal of residual $CHCl_3$ (δ 7.25).
[b]Overlapped signal.
[c]Collapsed into a singlet after addition of D_2O.
[d]*Exo* hydrogen with respect to ring B, except for **11** and **13**.
[e]*Endo* hydrogen with respect to ring B, except for **11** and **13**.
[f]Disappeared after addition of D_2O.
[g]Not observed.

Table 3
^{13}C NMR Spectral data of compounds **8**, **10**, **12**-**14**, **18**, **23**, **25**-**32**, **35** and **36**[a]

C	**8**	**10**	**12**	**13**	**14**	**18**	**23**[b]	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**35**	**36**
1	25.6 t	23.4 t	24.3 t	22.9 t	22.1 t	23.3 t	23.2 t	23.5 t	22.6 t	23.7 t	23.0 t	23.4 t	23.8 t	22.9 t	22.4 t	23.2 t	20.8 t
2	24.3 t	24.7 t	24.9 t	21.1 t	24.8 t	24.4 t	25.9 t	25.9 t	25.7 t	25.5 t	25.0 t	25.7 t	25.4 t	24.8 t	25.0 t	26.1 t	21.7 t
3	32.1 t	32.8 t	32.5 t	30.6 t	31.8 t	32.0 t	31.1 t	31.5 t	30.6 t	32.7 t	32.2 t	32.8 t	32.8 t	32.1 t	31.7 t	32.1 t	26.1 t
4	63.8 s	63.5 s	63.7 s	73.7 s	61.1 s	60.3 s	s	60.4 s	60.7 s	65.6 s	65.1 s	60.8 s	64.5 s	64.1 s	65.4 s	67.3 s	58.1 s
5	50.2 s	43.9 s	51.1 s	52.8 s	50.5 s	50.3 s	s	54.4 s	54.3 s	50.4 s	49.4 s	49.6 s	49.9 s	48.9 s	49.2 s	45.7 s	52.8 s[c]
6	78.7 d	69.5 d	72.4 d	70.6 d	185.4 s	186.8 s	s	200.2 s	200.1 s	78.0 d	78.7 d	190.0 s	75.9 d	76.6 d	72.8 d	76.6 d	78.8 d
7	104.3 s	138.0 s	107.8 s	106.7 s	143.8 s[c]	142.5 s[c]	69.6 d	75.3 d	77.1 d	206.8 s	205.4 s	133.4 s	201.9 s	200.8 s	209.6 s	74.2 d	111.5 s
8	46.9 d	128.4 s	41.0 d	41.3 d	145.1 s[c]	139.2 s[c]	44.9 d[c]	42.7 d	40.9 d	52.5 d	51.1 d	124.5 s	52.9 d	51.6 d	46.9 d	44.6 d	48.5 d
9	52.6 s	54.0 s	55.9 s	54.9 s	55.0 s	54.1 s	s	51.1 s	53.6 s	57.6 s	56.0 s	54.6 s	56.8 s	56.0 s	56.9 s	52.3 s	53.7 s[c]
10	51.8 d	48.5 d	47.9 d	44.5 d	50.3 d	49.5 d	44.8 d[c]	45.2 d	50.7 d	50.2 d	50.6 d	49.0 d	50.6 d	51.2 d	45.4 d	51.6 d	51.1 d
11	48.3 t	45.1 t	44.5 t	43.7 t	42.8 t	43.8 t	46.7 t	46.7 t	49.3 t	45.9 t	46.4 t	44.2 t	45.5 t	45.8 t	44.4 t	45.8 t	46.8 t
12	71.1 d	71.1 d	72.0 d	72.0 d	74.7 d	72.6 d	73.0 d	69.6 d	71.6 d	70.4 d	68.7 d	71.5 d	70.4 d	69.5 d	72.4 d	69.2 d	69.0 d
13	124.8 s	126.6 s	129.0 s	128.5 s	127.2 s	124.4 s	s	127.7 s	127.9 s	124.7 s	125.5 s	124.6 s	124.7 s	126.1 s	128.3 s	125.3 s	125.2 s
14	108.0 d	108.7 d	109.4 d	108.3 d	108.4 d	107.7 d	108.3 d	108.5 d	109.2 d	108.6 d	108.7 d	108.6 d	108.6 d	108.7 d	109.1 d	108.8 d	108.7 d
15	144.2 d	143.5 d	143.5 d	142.1 d	143.7 d	144.5 d	143.5 d	143.6 d	143.5 d	143.5 d	143.6 d	143.6 d	143.4 d	143.6 d	143.7 d	143.2 d	143.4 d
16	139.6 d	139.3 d	139.6 d	138.2 d	139.0 d	139.6 d	138.1 d	138.1 d	139.8 d	139.5 d	139.6 d	139.5 d	139.3 d	139.4 d	139.8 d	139.4 d	139.5 d
17	9.2 q	14.8 q	15.5 q	14.1 q	17.1 q	14.5 q	8.4 q	10.0 q	12.4 q	9.7 q	10.4 q	14.2 q	9.7 q	10.5 q	18.2 q	14.3 q	8.9 q
18	53.2 t	51.6 t	53.2 t	74.6 t	50.8 t	48.2 t	50.0 t	50.2 t	52.4 t	51.4 t	49.9 t	50.8 t	51.5 t	50.0 t	51.5 t	49.3 t	48.0 t
19	66.0 t	63.2 t	66.6 t	64.5 t	63.2 t	62.8 t	62.2 t	62.5 t	62.4 t	62.0 t	62.2 t	64.0 t	61.5 t	61.8 t	61.3 t	63.6 t	67.5 t
20	173.9 s	106.6 d	106.6 d	105.6 d	98.9 d	174.4 s	106.9 d	106.7 d	106.3 d	106.8 d	106.0 d	110.6 d	106.9 d	106.0 d	104.7 d	107.4 d	106.8 d
OAc	-	170.3 s	-	-	169.9 s	170.5 s	s	170.3 s	170.5 s	169.9 s	170.5 s	170.2 s	169.9 s	170.2 s	169.7 s	-	169.4 s
	-	170.2 s	-	-	169.1 s	168.0 s	20.8 q	169.9 s	170.2 s	20.7 q	21.0 q	20.8 q	169.8 s	169.9 s	20.3 q	-	167.9 s
	-	167.9 s	-	-	168.3 s	20.8 q	-	20.9 q	21.0 q	-	-	-	20.4 q	20.7 q	-	-	20.8 q
	-	21.1 q	-	-	20.9 q	20.0 q	-	20.5 q	20.5 q	-	-	-	20.4 q	20.5 q	-	-	20.7 q
	-	20.6 q	-	-	20.4 q	-	-	-	-	-	-	-	-	-	-	-	-
	-	20.2 q	-	-	20.1 q	-	-	-	-	-	-	-	-	-	-	-	-
18-OMe	-	-	-	58.1 q	-	-	-	-	-	-	-	-	-	-	-	-	-
20-OMe	-	57.0 q	54.9 q	53.3 q	-	-	53.7 q	53.8 q	54.3 q	54.0 q	57.3 q	54.6 q	53.8 q	56.5 q	54.6 q	54.3 q	54.1 q

[a]At 125.7 MHz (**8**, **12**, **27**, **28** and **32**) or 50.3 MHz (**10**, **13**, **14**, **18**, **23**, **25**, **26**, **29**-**31**, **35** and **36**) in $CDCl_3$ solution, except for **13** [$CDCl_3$-pyridine-d_5 (1:1)]. Chemical shifts (δ values) are reported with respect to the solvent signals (δ 77.00). All these assignments were in agreement with HMQC and DEPT spectra and, in some cases (**8**, **12**, **27**, **28** and **32**), also with HMBC spectra.

[b]For this compound only protonated carbons were measured by a DEPT pulse sequence experiment (see Discussion of results).

[c]Assignments within the same column may be interchanged, but those given here are considered to be the most likely.

hydroxy-18-methoxy-neocleroda-7,13(16),14-triene-20,12-(20-O-methyl)acetal (**11**) *from peracetylisoeriocephalin* (**4**).

To a solution of **4** (130 mg, 0.238 mmol) in a mixture of toluene (50 mL) and MeOH (5 mL) was added *p*-TsOH.H_2O(2 mg, 0.01 mmol) and the reaction mixture was subjected to microwave irradiation in a domestic microwave oven for 4 successive periods of 1 min each, using a potence of 100 W [28] and an open vessel. CAUTION: between each irradiation period the reaction mixture was cooled to 15 °C. Then the reaction was diluted with EtOAc (75 mL), washed with an aqueous solution of $NaHCO_3$ (10%, w/v) and the organic layer dried (Na_2SO_4) and evaporated to dryness yielding a residue (112 mg) which was subjected to column chromatography (Si gel, 15 g). Elution with EtOAc-petrol (2:1) gave **10** (99 mg, 0.191 mmol, less polar constituent, 80% yield) and **11** (10 mg, 0.018 mmol, 7.6%). When the irradiation was continued for a further 20 min only compound **11** was obtained.

Compound **10**: amorphous white solid, mp 55-70 °C; $[\alpha]_D^{18}$ +19.6° (*c* 0.424, $CHCl_3$). IR (KBr) ν_{max} cm^{-1}: 3140, 3120, 1500, 870 (furan), 3020 (oxirane), 1760, 1740, 1250, 1230 (OAc), 2950, 2860, 1445, 1370, 1200, 1085, 1050, 1025, 915. ^1H NMR: see Table 2. ^{13}C NMR: see Table 3. EIMS *m/z* (rel. int.): 518 $[M]^+$ (0.02), 487 (0.1), 458 (0.6), 427 (0.2), 416 (4), 374 (3), 314 (6), 296 (7), 283 (12), 265 (10), 173 (5), 145 (7), 95 (17), 94 (12), 91 (6), 85 (15), 81 (13), 55 (8), 47 (9), 43 (100). (Anal. Found: C, 62.47; H, 6.53%. $C_{27}H_{34}O_{10}$ requires: C, 62.54; H, 6.61%).

Compound **11**: colourless crystalline solid, mp 152-154 °C (EtOAc - *n*-hexane); $[\alpha]_D^{17}$ +13.6° (*c* 0.022, $CHCl_3$). IR (KBr) ν_{max} cm^{-1}: 3460 (OH), 3140, 1505, 875 (furan), 1760, 1740, 1250, 1230 (OAc), 2940, 2860, 2830, 1450, 1370, 1200, 1110, 1050, 1025, 905, 815, 800. ^1H NMR: see Table 2. EIMS *m/z* (rel. int.): 550 $[M]^+$ (0.1), 519 (0.2), 490 (0.2), 448 (6), 430 (4), 406 (6), 388 (9), 370 (19), 343 (18), 328 (32), 297 (49), 283 (34), 265 (31), 213 (42), 161 (28), 115 (20), 95 (38), 94 (27), 91 (15), 81 (32), 55 (17), 45 (35), 43 (100). (Anal. Found: C, 60.87; H, 6.99%. $C_{28}H_{38}O_{11}$ requires: C, 61.08; H, 6.96%).

Preparation of (12S,20R)-4α,18;7α,19;15,16-triepoxy-6α,7β-dihydroxy-17β-neocleroda-13(16),14-diene-20,12-(20-O-methyl)acetal (**12**) *and (12S,20R)-7α,19;15,16-diepoxy-4α,6α,7β-trihydroxy-18-methoxy-17β-neocleroda-13(16),14-diene-20,12-(20-O-methyl) acetal* (**13**) *from compound* **10.**

A mixture of **10** (350 mg, 0.675 mmol) and Na_2CO_3 (150 mg, 1.415 mmol) in MeOH solution (200 mL) was refluxed for 3 h. The solvent was evaporated under reduced pressure and low temperature (35 °C) and the residue was digested with $CHCl_3$ (4 x 10 mL). The chloroform extract was evaporated to dryness yielding a residue (280 mg) which was sujected to column chromatography (Si gel, 40 g, $CHCl_3$-MeOH 97:3 as eluent) giving **12** (228 mg, 0.581 mmol, less polar constituent, 86% yield) and **13** (22 mg, 0.051 mmol, 7.7%).

Compound **12**: colourless crystalline solid, mp 214-217 °C (EtOAc - *n*-hexane); $[\alpha]_D^{17}$ -17.5° (*c* 0.143, $CHCl_3$). IR (KBr) ν_{max} cm^{-1}: 3540, 3390 (OH), 3140, 3110, 1500, 870 (furan), 2980, 2950, 2860, 2820, 1465, 1380, 1330, 1220, 1100, 1035, 1020, 1005, 975, 955, 910, 890, 850, 800. ^1H NMR: see Table 2. ^{13}C NMR: see Table 3. EIMS *m/z* (rel. int.): 392 $[M]^+$ (0.8), 374 (3), 361 (11), 343 (10), 313 (11), 283 (10), 245 (17), 239 (10), 220 (19), 219 (15), 203 (12), 190 (23), 175 (22), 173 (20), 163 (52), 161 (36), 145 (39), 135 (41), 124

(58), 95 (85), 94 (100), 91 (71), 81 (93), 55 (60), 53 (44), 43 (31). (Anal. Found: C, 64.52; H, 7.31%. $C_{21}H_{28}O_7$ requires: C, 64.27; H, 7.19%).

Compound **13**: colourless crystalline solid, mp 202-204 °C (EtOAc - *n*-hexane); $[\alpha]_D^{17}$ -33.8° (*c* 0.514, $CHCl_3$). IR (KBr) ν_{max} cm^{-1}: 3480, 3360, 3160 (OH), 1500, 870 (furan), 2960, 2880, 2820, 1450, 1385, 1375, 1325, 1200, 1195, 1165, 1105, 1060, 1045, 1020, 1000, 980, 930, 915, 835, 820, 790, 755. ^1H NMR: see Table 2. ^{13}C NMR: see Table 3. EIMS *m/z* (rel. int.): 424 $[M]^+$ (2), 406 (2), 393 (12), 375 (9), 347 (45), 329 (12), 317 (11), 314 (11), 299 (15), 283 (15), 265 (11), 233 (15), 189 (28), 177 (26), 175 (26), 163 (100), 159 (25), 147 (50), 145 (45), 135 (68), 124 (39), 121 (47), 105 (38), 95 (74), 94 (60), 93 (49), 91 (58), 81 (92), 79 (62), 67 (47), 55 (78), 45 (100), 43 (48), 41 (47). (Anal. Found: C, 62.09; H, 7.49%. $C_{22}H_{32}O_8$ requires: C, 62.25; H, 7.60%).

Compound **13** *from compound* **11**.

Treatment of **11** (5 mg, 0.009 mmol) with Na_2CO_3 in MeOH solution as described above for **10** yielded **13** (3 mg, 0.007 mmol, 77%), identified by its mp, ^1H NMR and MS. Comparison (mixed mp, TLC) with an authentic sample confirmed the identity.

7-O-Acetyl-7,8-didehydroeriocephalin (**14**) *from 7,8-didehydroeriocephalin* (**15**).

Ac_2O-pyridine (20 mL, 1:1) treatment of **15** (200 mg, 0.434 mmol)[24] for 24 h at room temperature and work-up in the usual manner yielded **14** (218 mg, 0.434 mmol, quantitative yield): colourless crystalline solid, mp 182-184 °C decomp. (EtOAc - *n*-hexane); $[\alpha]_D^{19}$ -89.1° (*c* 0.311, $CHCl_3$). UV (MeOH) λ_{max} nm (log ε): 212 (3.81), 246.5 (4.09). IR (KBr) ν_{max} cm^{-1}: 3140, 3120, 1505, 875 (furan), 1760, 1730, 1245, 1215 (OAc), 1685, 1640 (diosphenol), 2940, 2910, 2870, 1440, 1370, 1150, 1100, 1060, 1020, 970, 960, 910, 800. ^1H NMR: see Table 4. ^{13}C NMR: see Table 3. EIMS *m/z* (rel. int.): 502 $[M]^+$ (0.3), 443 (6), 383 (2), 341 (6), 312 (5), 299 (6), 281 (8), 253 (5), 215 (5), 203 (5), 177 (5), 161 (5), 145 (5), 121 (5), 105 (7), 95 (11), 94 (36), 91 (11), 81 (15), 43 (100). (Anal. Found: C, 62.18; H, 6.11%. $C_{26}H_{30}O_{10}$ requires: C, 62.14; H, 6.02%).

Sodium borohydride reduction of compound **14** *to give compound* **16**.

Compound **14** (33 mg, 0.065 mmol) in MeOH-dioxane solution (8 mL, 3:1) was treated with an excess of $NaBH_4$ (30 mg, 0.793 mmol) at room temperature for 15 min. Work-up in the usual manner gave **16** (30 mg, 0.059 mmol, 90% yield): colourless crystalline solid, mp 217-218 °C (EtOAc - *n*-hexane); $[\alpha]_D^{18}$ -45.1° (*c* 0.162, $CHCl_3$). The derivative **16** was identical (IR, ^1H NMR and MS) to a compound previously obtained [14] by reduction of **5**; (lit. [14] **16**: mp 210-212 °C, from $CHCl_3$ - *n*-hexane; $[\alpha]_D^{26}$ -46.3°, *c* 0.564, $CHCl_3$). Comparison (mixed mp, TLC) with an authentic sample confirmed the identity.

Sodium borohydride-cerium trichloride reduction of compound **14** *to give compound* **5**.

Compound **14** (150 mg, 0.3 mmol) in MeOH solution (30 mL) was treated with $NaBH_4$ (45 mg, 1.2 mmol) and $CeCl_3.7H_2O$ (447 mg, 1.2 mmol) for 3 h at room temperature. Work-up in the usual manner yielded **5** (130 mg, 0.26 mmol, after crystallisation from EtOAc - *n*-hexane, 86%), identical in all respects (mp, $[\alpha]_D$, IR, ^1H NMR, MS, TLC) with 6-*O*-

Table 4
^{1}H NMR Spectral data for compounds **14**, **18**, **23**, and **25-28**[a]

H	14	18	23	25	26	27	28	$J_{H,H}$ (Hz)	14	18	23	25	26	27	28
1α	[b]	[b]	[b]	1.86 dddd	1.62 dddd	2.47 dddd	1.92 dddd	1α,1β	[b]	[b]	[b]	12.5	13.2	13.6	13.7
1β	[b]	[b]	[b]	[b]	1.96 br d	2.06 dddd	[b]	1α,2α	[b]	[b]	[b]	3.5	3.9	3.6	3.5
2α	[b]	[b]	[b]	[b]	2.05 ddddd	[b]	[b]	1α,2β	[b]	[b]	[b]	13.5	13.4	13.4	13.4
2β	[b]	[b]	[b]	1.34 qt	1.50 qt	1.37 qt	1.57 qt	1α,10β	11.1	12.0	[b]	12.0	12.3	12.2	10.6
3α	[b]	2.38 dddd	[b]	[b]	2.27 dddd	[b]	[b]	1β,2α	[b]	[b]	[b]	[b]	3.4	3.8	[b]
3β	1.16 m	1.02 ddd	[b]	1.15 ddd	1.17 ddd	1.19 ddd	1.21 dt	1β,2β	[b]	[b]	[b]	4.4	4.9	3.8	3.2
6β	-	-	-	-	-	4.03 t[c]	4.02 br t[d]	1β,10β	4.4	4.0	[b]	2.0	2.3	2.7	5.0
7β	-	-	4.80 dd[e]	5.65 d	5.57 d	-	-	2α,2β	[b]	[b]	[b]	13.5	13.4	13.4	13.4
8β	-	-	[b]	2.18 qd	2.48 qd	2.39 qd	2.37 qd	2α,3α	[b]	5.0	[b]	[b]	5.4	[b]	[b]
10β	2.47 dd	2.48 dd	[b]	2.62 dd	2.40 dd	2.18 dd	2.15 dd	2α,3β	[b]	4.8	[b]	3.1	1.7	2.9	2.9
11A	2.34 dd	2.59 dd	1.91 dd	1.89 dd	2.42 dd	1.92 dd	2.22 dd	2β,3α	[b]	12.0	[b]	13.5	13.9	13.4	13.4
11B	2.74 dd	2.76 dd	2.78 dd	2.82 dd	2.57 dd	2.47 dd	2.27 dd	2β,3β	[b]	2.1	[b]	4.4	4.9	3.8	3.8
12	5.31 br t	5.56 br t	5.09 dd	5.11 dd	5.08 t	4.97 dd	4.70 dd	3α,3β	13.0	14.2	[b]	13.0	13.9	13.3	13.4
14	6.39 dd	6.36 dd	6.30 dd	6.32 dd	6.41 dd	6.41 dd	6.43 dd	6β,8β	-	-	-	-	-	1.6	1.5
15	7.41 t	7.43 t	7.37 t	7.40 t	7.37 t	7.40 t	7.39 t	7β,8β	-	-	6.9	6.4	4.9	-	-
16	7.36 m	7.46 m	7.35 m	7.37 m	7.39 m	7.42 m	7.40 m	8β,17	-	-	7.4	7.3	7.3	6.8	6.6
Me-17	2.00 s	1.74 s	0.91 d	1.07 d	1.14 d	1.18 d	1.40 d	11A,11B	14.0	14.6	12.2	12.3	12.7	13.2	13.7
18A[f]	2.41 d	2.25 d	2.41 d	2.37 d	2.38 d	2.56 d	2.53 d	11A,12	8.7	8.6	4.4	4.1	8.3	10.4	7.4
18B[g]	2.75 dd	2.91 dd	2.31 dd	3.03 dd	2.87 dd	3.28 dd	3.20 dd	11B,12	6.9	8.2	9.5	9.7	8.1	6.7	9.3
19A	4.47 d	4.84 d	4.61 d	4.59 d	4.63 d	4.23 d	4.31 d	14,15	1.8	1.9	1.8	1.8	1.8	1.8	1.8
19B	4.69 d	4.95 d	4.67 d	4.64 d	4.68 d	4.70 d	4.55 br d	14,16	0.8	0.9	0.9	0.8	0.9	0.8	0.8
20	6.40 s	-	4.93 s	4.96 s	4.80 s	4.60 s	4.84 s	15,16	1.8	1.9	1.8	1.8	1.8	1.8	1.8
6α-OH[h]	-	-	-	-	-	3.67 d	3.79 d	18A,18B	4.5	5.0	3.8	3.8	3.9	3.5	3.5
7α-OH[h]	-	-	3.42 d	-	-	-	-	18B,3α	2.0	2.2	2.1	2.3	2.2	2.3	2.3
OAc	2.22 s	2.16 s	2.08 s	2.11 s	2.13 s	1.98 s	2.07 s	19A,19B	11.7	12.5	11.8	11.7	12.2	11.4	12.2
	1.94 s	2.02 s	-	2.08 s	2.10 s	-	-	19B,6β	-	-	-	-	-	0	<0.3
	1.93 s	-	-	-	-	-	-	6β,6-OH[h]	-	-	-	-	-	1.9	1.5
20-OMe	-	-	3.27 s	3.29 s	3.29 s	3.19 s	3.35 s	7β,7-OH[h]	-	-	5.2	-	-	-	-

[a]At 200 MHz (**14**, **18** and **23**) or 500 MHz (**25-28**) in $CDCl_3$ solution. Chemical shifts (δ values) are reported with respect to the signal of residual $CHCl_3$ (δ 7.25).
[b]Overlapped signal.
[c]Collapsed into a doublet (J= 1.6 Hz) after addition of D_2O.
[d]Collapsed into a broad doublet (J= 1.5 Hz) after addition of D_2O.
[e]Collapsed into a doublet (J= 6.9 Hz) after addition of D_2O.
[f]*Exo* hydrogen with respect to ring B.
[g]*Endo* hydrogen with respect to ring B.
[h]Disappeared after addition of D_2O.

acetylisoeriocephalin (**5**)[14]. The derivative **5** was also obtained from 7-*O*-acetyleriocephalin (**17**)[14] by a thermal α-ketol rearrangement as previously described [26] for other 6-oxo-7α-acetoxy-neoclerodane derivatives. This rearrangement was carried-out by heating a small sample of **17** (2 mg) on a Kofler block at 130 °C for 3 min. TLC analysis revealed the presence of **5** and starting material (**17**) in 1:1 ratio.

7-O-Acetylpicropolinone (**18**) *from picropolinone* (**19**).

Ac_2O-pyridine (10 mL, 1:1) treatment of **19** (150 mg, 0.360 mmol)[18-20] for 24 h at room temperature and work-up in the usual manner gave **18** (138 mg, 0.301 mmol, 83% yield): colourless crystalline solid, mp 197-199 °C (EtOAc - *n*-hexane); $[\alpha]_D^{20}$ +38.3° (*c* 0.478, $CHCl_3$). UV (MeOH) λ_{max} nm (log ε): 209 (3.97), 246 (4.06). IR (KBr) ν_{max} cm^{-1}: 3160, 3130, 1505, 875 (furan), 1765 (γ-lactone), 1760, 1730, 1260 (OAc), 1700, 1660 (diosphenol), 2960, 2880, 1470, 1370, 1170, 1160, 1025, 920, 730, 690. ^1H NMR: see Table 4. ^{13}C NMR: see Table 3. EIMS *m/z* (rel. int.): 458 $[M]^+$ (0.05), 399 (0.1), 398 (0.05), 338 (0.2), 326 (4), 250 (4), 205 (4), 177 (7), 121 (12), 95 (14), 94 (18), 91 (11), 81 (16), 55 (8), 43 (100). (Anal. Found: C, 62.91; H, 5.64%. $C_{24}H_{26}O_9$ requires: C, 62.87; H, 5.72%).

Sodium borohydride reduction of compound **18** *to give compound* **20**.

Treatment of a solution of **18** (85 mg, 0.185 mmol) in MeOH-dioxane (10 mL, 3:1) with $NaBH_4$ (50 mg, 1.321 mmol) at room temperature for 15 min quantitatively yielded **20**: colourless crystalline solid, mp 275-278 °C (EtOAc); $[\alpha]_D^{21}$ +19.6° (*c* 0.136, $CHCl_3$-MeOH 1:1), IR, ^1H NMR and MS identical to those reported for the derivative obtained by $NaBH_4$ reduction of **21** (lit. [25] **20**: mp 275-278 °C; $[\alpha]_D^{21}$ +19.8°, *c* 0.121, $CHCl_3$-MeOH 1:1).

Sodium borohydride-boric acid reduction of compound **18** *to give 6-O-acetylpicropolin* (**9**).

To a solution of **18** (40 mg, 0.087 mmol) and H_3BO_3 (80 mg, 1.293 mmol) in MeOH (20 mL) an excess of $NaBH_4$ (100 mg, 2.642 mmol) was added in portions with stirring and the reaction mixture was kept for 30 min at room temperature. Then, the reaction was diluted with H_2O (50 mL) and extracted with EtOAc (4 x 20 mL). Work-up in the usual manner gave **9** (34 mg, 0.074 mmol, 84% yield), identical in all respects (mp, IR, ^1H NMR, MS and TLC) with the compound described above and previously obtained by acetylation of picropolin (**7**)[17] and by thermal rearrangement of capitatin (**21**)[26].

Preparation of (12S,20S)- (**23**) *and (12S,20R)-19-acetoxy-4α,18;15,16-diepoxy-7α-hydroxy-6-oxo-neocleroda-13(16),14-diene-20,12-(20-O-methyl)acetal* (**24**) *and their corresponding acetates* (**25** *and* **26**) *from eriocephalin* (**22**).

A solution of **22** (160 mg, 0.346 mmol)[14,27] and *p*-TsOH.H_2O (2 mg, 0.01 mmol) in a mixture of toluene (15 mL) and MeOH (3 mL) was irradiated in a domestic microwave oven for 3 successive periods of 2 min each in the conditions described above for **4**. Work-up as described above yielded a crude of reaction (140 mg) which showed two spots on TLC, both less polar than **22**. Column chromatography of this mixture (Si gel, EtOAc-petrol 1:1 as eluent) allowed the isolation of the less polar constituent (**23**, 36 mg, 0.083 mmol, 24% yield) and a mixture of other two compounds, both of them different from the second constituent

(**24**) of the initial mixture. Compound **23** was an unstable substance which was slowly transformed into another compound (**27**, see below) on storage or in $CHCl_3$, Me_2CO or MeOH solutions. For the ^1H and ^{13}C NMR spectra of **23** see Tables 4 and 3, respectively.

A fresh amount (160 mg) of the crude of the above reaction was treated with Ac_2O-pyridine (10 mL, 1:1) for 48 h at room temperature giving **25** (92 mg, 0.193 mmol, less polar constituent, 52% yield) and **26** (52 mg, 0.109 mmol, 29%) after column chromatography (Si gel, petrol-EtOAc 7:3 as eluent).

Acetylation of **23** (1 mg) in the same conditions yielded **25**, identified by TLC.

Compound **25**: amorphous white solid, mp 80-87 °C; $[\alpha]_D^{18}$ +135.1° (*c* 0.339, $CHCl_3$). IR (KBr) ν_{max} cm^{-1}: 3140, 1500, 875 (furan), 1750, 1250, 1230 (OAc), 1730 (ketone), 2940, 2880, 1450, 1370, 1160, 1110, 1070, 1030, 970, 915, 865, 790, 755. ^1H NMR: see Table 4. ^{13}C NMR: see Table 3. EIMS *m/z* (rel. int.): 476 $[M]^+$ (0.05), 445 (0.08), 371 (0.7), 283 (2), 190 (3), 189 (3), 163 (5), 161 (6), 147 (5), 121 (8), 95 (25), 94 (93), 91 (11), 81 (21), 55 (11), 43 (100). (Anal. Found: C, 62.81; H, 6.93%. $C_{25}H_{32}O_9$ requires: C, 63.01; H, 6.77%).

Compound **26**: colourless crystalline solid, mp 219-221 °C (EtOAc - *n*-hexane); $[\alpha]_D^{20}$ +43.4° (*c* 0.214, $CHCl_3$). IR (KBr) ν_{max} cm^{-1}: 3140, 3120, 1505, 875 (furan), 1755, 1745, 1230 (OAc), 1735 (ketone), 2960, 1475, 1455, 1390, 1370, 1160, 1090, 1050, 1020, 800, 750, 640, 630. ^1H NMR: see Table 4. ^{13}C NMR: see Table 3. EIMS *m/z* (rel. int.): 476 $[M]^+$ (0.1), 445 (0.7), 416 (0.3), 371 (0.4), 343 (0.8), 329 (0.7), 283 (1), 265 (1), 190 (2), 175 (2), 173 (2), 163 (4), 161 (5), 125 (22), 95 (17), 94 (100), 91 (7), 81 (16), 43 (69). (Anal. Found: C, 62.93; H, 6.59%. $C_{25}H_{32}O_9$ requires: C, 63.01; H, 6.77%).

Preparation of (12S,20S)- (**27**) *and (12S,20R)-19-acetoxy-4α,18;15,16-diepoxy-6α-hydroxy-7-oxo-neocleroda-13(16),14-diene-20,12-(20-O-methyl)acetal* (**28**) *from the mixture of compounds* **23** *and* **24**.

To a solution of the mixture **23** and **24** (450 mg, 1.036 mmol) in EtOAc (250 mL) was added Si gel (Merck, No. 7734, previously activated at 140 °C for 2 h, 30 g) and the mixture was stirred at room temperature for 55 h. Then, Si gel was removed by filtration through a pad of Celite and the solvent evaporated. The residue (443 mg) was subjected to column chromatography (Si gel, EtOAc-petrol 3:2 as eluent) giving **27** (266 mg, 0.613 mmol, 59% yield, less polar constituent) and **28** (164 mg, 0.377 mmol, 36%).

Compound **27**: colourless crystalline solid, mp 204-206 °C (EtOAc - *n*-hexane); $[\alpha]_D^{18}$ +67.5° (*c* 0.504, $CHCl_3$). IR (KBr) ν_{max} cm^{-1}: 3440 (OH), 3160, 3130, 3120, 1510, 880 (furan), 3050 (oxirane), 1730, 1240 (OAc), 1715 (ketone), 2980, 2920, 2860, 1450, 1370, 1130, 1035, 1020, 1000, 930, 830, 800, 760. ^1H NMR: see Table 4. ^{13}C NMR: see Table 3. EIMS *m/z* (rel. int.): 434 $[M]^+$ (0.1), 374 (0.5), 361 (1.7), 301 (0.4), 287 (2.5), 255 (3), 227 (4), 219 (4), 189 (5), 175 (6), 163 (16), 161 (12), 145 (16), 135 (13), 133 (12), 121 (10), 105 (12), 95 (24), 94 (84), 91 (19), 81 (48), 79 (27), 67 (18), 55 (16), 53 (12), 43 (100), 41 (14). (Anal. Found: C, 63.21; H, 6.93%. $C_{23}H_{30}O_8$ requires: C, 63.58; H, 6.96%).

Compound **28**: colourless crystalline solid, mp 219-222 °C (EtOAc - *n*-hexane); $[\alpha]_D^{18}$ -43.3° (*c* 0.374, $CHCl_3$). IR (KBr) ν_{max} cm^{-1}: 3490 (OH), 3140, 3120, 1500, 880 (furan), 3050 (oxirane), 1735, 1260 (OAc), 1720 (ketone), 2950, 2880, 1450, 1370, 1160, 1125, 1050, 1025, 1005, 925, 895, 810. ^1H NMR: see Table 4. ^{13}C NMR: see Table 3. EIMS *m/z* (rel. int.):

$[M]^+$ absent, 374 $[M\text{-}AcOH]^+$ (1.2), 361 $[M\text{-}CH_2OAc]^+$ (0.5), 301 $[M\text{-}AcOH\text{-}CH_2OAc]^+$ (0.5), 287 (3), 255 (3), 233 (3), 227 (3), 219 (3), 209 (4), 189 (5), 173 (7), 163 (11), 161 (10), 147 (13), 145 (15), 135 (12), 131 (11), 123 (12), 119 (13), 107 (14), 105 (19), 95 (62), 94 (100), 91 (38), 81 (68), 79 (32), 77 (22), 67 (16), 55 (15), 53 (12), 43 (65), 41 (19). (Anal. Found: C, 63.18; H, 6.93%. $C_{23}H_{30}O_8$ requires: C, 63.58; H, 6.96%).

Microwave irradiation of isoeriocephalin (**3**) *to give compounds* **27** *and* **28**.

Treatment of **3** (100 mg, 0.216 mmol)[14] as previously described for **22** gave **27** and **28** in low yield (10 and 6%, respectively), together with several decomposition products. Attempts at improving this reaction were unsuccessful.

Treatment of **27** *with 1,4-diazabicyclo[2.2.2]octane to give (12S,20S)-19-acetoxy-4α,18;15,16-diepoxy-7-hydroxy-6-oxo-neocleroda-7,13(16),14-triene-20,12-(20-O-methyl) acetal* (**29**).

A solution of **27** (160 mg, 0.368 mmol) and DABCO (30 mg, 0.267 mmol) in toluene (100 mL) was heated at 120 °C for 10 h. Evaporation of the solvent and column chromatography (Si gel, petrol-EtOAc 1:1 as eluent) yielded **29** (10 mg, 0.023 mmol, less polar compound, 6.3%) and starting material (**27**, 136 mg, 0.313 mmol, 85%). When this reaction was carried out under Ar only starting material (**27**) was recovered.

Compound **29**: colourless crystalline solid, mp 163-165 °C (EtOAc - *n*-hexane); $[\alpha]_D^{18}$ +49.2° (*c* 0.413, $CHCl_3$). UV (EtOH) λ_{max} nm (log ε): 207 (3.81), 281 (4.05). IR (KBr) ν_{max} cm^{-1}: 3380 (OH), 3140, 3120, 1505, 880 (furan), 3060 (oxirane), 1740, 1240 (OAc), 1675, 1640 (diosphenol), 2940, 1450, 1390, 1370, 1290, 1160, 1140, 1050, 1030, 1020, 985, 805, 785, 700, 650. ^1H NMR: see Table 5. ^{13}C NMR: see Table 3. EIMS *m/z* (rel. int.): 432 $[M]^+$ (0.03), 372 $[M\text{-}AcOH]^+$ (1.5), 357 (1), 312 (3), 299 (10), 281 (14), 263 (7), 219 (17), 177 (19), 159 (12), 131 (11), 105 (10), 95 (19), 94 (20), 91 (22), 81 (37), 77 (21), 69 (10), 55 (20), 43 (100). (Anal. Found: C, 64.17; H, 6.63%. $C_{23}H_{28}O_8$ requires: C, 63.88; H, 6.53%).

Acetic anhydride-pyridine treatment of **27**: *derivative* **30**.

Ac_2O-pyridine (10 mL, 1:1) treatment of **27** (80 mg, 0.184 mmol) for 48 h at room temperature and work-up as usual (elimination of the volatiles in rotavapor at 70 °C) yielded **30** (79 mg, 0.166 mmol, 90%) as an amorphous white solid: mp 55-65 °C; $[\alpha]_D^{19}$ +72.9° (*c* 0.837, $CHCl_3$). IR (KBr) ν_{max} cm^{-1}: 3140, 1505, 875 (furan), 3050 (oxirane), 1740, 1250 (OAc), 1730 (ketone), 2940, 1450, 1370, 1120, 1050, 1030, 1000, 980, 925. ^1H NMR: see Table 5. ^{13}C NMR: see Table 3. EIMS *m/z* (rel. int.): 476 $[M]^+$ (0.04), 416 $[M\text{-}AcOH]^+$ (1.3), 401 (0.4), 385 (1), 361 (4), 296 (5), 283 (4), 268 (4), 239 (5), 227 (5), 187 (5), 175 (6), 173 (6), 163 (10), 159 (12), 145 (14), 105 (12), 95 (32), 94 (73), 91 (32), 81 (26), 77 (11), 55 (16), 43 (100). (Anal. Found: C, 63.12; H, 6.58%. $C_{25}H_{32}O_9$ requires: C, 63.01; H, 6.77%).

Acetic anhydride-pyridine treatment of **28**: *compounds* **10** *and* **31**.

Treatment of **28** (70 mg, 0.161 mmol) with Ac_2O-pyridine (8 mL, 1:1) as in the case of **27** (see above) gave a mixture of two compounds (TLC), which were separated by column chromatography (Si gel, petrol-EtOAc 1:1 as eluent) yielding **10** (8 mg, 0.015 mmol, 9.5%)

and **31** (60 mg, 0.126 mmol, most polar constituent, 78%). The derivative **10** was identified by its $[\alpha]_D$, ^{1}H NMR and MS and by comparison (TLC) with the compound described above.

Table 5
^{1}H NMR Spectral data for compounds **29-32**, **35** and **36**[a]

H	29	30	31	32	35	36	J_{HH} (Hz)	29	30	31	32	35	36
1α	2.44[b]	[b]	[b]	1.89 dddd	2.34 dddd	[b]	1α,1β	[b]	[b]	[b]	13.9	13.6	[b]
1β	[b]	[b]	[b]	1.81 dddd	1.87 dddd	[b]	1α,2α	[b]	[b]	[b]	3.9	3.5	[b]
2α	[b]	[b]	[b]	2.07 br d	1.97 br d	[b]	1α,2β	[b]	13.4	13.3	13.4	13.3	[b]
2β	1.32 m	1.37 qt	1.55 qt	1.53 qt	1.30 qt	[b]	1α,10β	[b]	12.3	[b]	12.5	12.6	11.8
3α	2.11 tdd	[b]	[b]	2.00 tdd	2.46 tdd	[b]	1β,2α	[b]	[b]	[b]	3.4	3.8	[b]
3β	1.18 dm	[b]	1.10 ddd	1.18 ddd	1.10 ddd	1.11 ddd	1β,2β	[b]	3.8	3.7	4.4	3.9	[b]
6β	-	5.03 br s	5.01 d	4.18 d[c]	3.51 dd	5.60 s	1β,10β	[b]	2.6	[b]	3.7	3.0	[b]
7β	-	-	-	-	3.89 dd	-	2α,2β	[b]	13.4	13.4	13.4	13.3	[b]
8α	-	-	-	3.38 q	-	-	2α,3α	4.5	[b]	[b]	4.4	4.3	[b]
8β	-	[b]	2.40 qd	-	1.43 qd	2.47 q	2α,3β	[b]	[b]	2.9	2.9	2.8	1.0
10β	[b]	2.22 dd	[b]	2.20 dd	1.54 dd	2.06 br d	2β,3α	13.4	13.4	13.4	13.4	13.3	[b]
11A	2.25 dd	1.92 dd	2.20 dd	2.12 dd	1.76 dd	1.83 dd	2β,3β	[b]	3.8	3.8	4.4	3.9	8.4
11B	2.34 dd	2.47 dd	2.32 dd	2.17 dd	2.22 dd	2.25 dd	3α,3β	13.4	[b]	13.4	13.4	13.3	14.5
12	5.12 dd	4.99 dd	4.78 br t	5.05 t	4.86 dd	4.93 dd	6β,7β	-	-	-	-	3.6	-
14	6.46 dd	6.41 dd	6.41 dd	6.38 dd	6.42 dd	6.41 dd	6β,8β	-	0.3	1.0	-	0	0
15	7.44 t	7.41 t	7.36 t	7.36 t	7.39 t	7.40 t	7β,8β	-	-	-	-	2.7	-
16	7.47 m	7.42 m	7.37 m	7.34 m	7.41 m	7.42 m	8α,17	-	-	-	7.6	-	-
Me-17	1.99 s	1.15 d	1.33 d	1.24 d	1.19 d	0.97 d	8β,17	-	6.8	6.6	-	7.2	7.2
18A[d]	2.40 d	2.40 d	2.34 d	2.61 d	2.43 d	2.44 d	11A,11B	13.5	13.2	13.8	13.4	13.1	13.2
18B[e]	2.56 dd	3.06 dd	2.95 dd	3.27 dd	3.19 dd	2.88 dd	11A,12	10.0	10.2	7.8	8.1	10.4	9.9
19A	4.52 d	4.35 d	4.38 d	4.29 d	4.33 dd	3.49 dd	11B,12	7.1	6.8	8.8	8.1	6.8	6.8
19B	4.64 d	4.83 d	4.64 d	4.73 d	4.58 d	4.15 d	14,15	1.9	1.7	1.7	1.7	1.8	1.8
20	4.79 s	4.62 s	4.87 s	4.83 s	5.36 s	5.29 s	14,16	0.8	0.8	0.9	0.7	0.9	0.8
6α-OH[f]	-	-	-	3.60 d	3.97 s	-	15,16	1.9	1.7	1.7	1.7	1.8	1.8
7α-OH[f]	-	-	-	-	3.02 s	-	18A,18B	4.6	3.4	3.7	3.7	3.5	4.5
7-OH[f]	6.40 s	-	-	-	-	-	18B,3α	2.2	2.7	2.1	2.4	2.4	0
19-OH[f]	-	-	-	-	3.02 s	-	19A,19B	11.2	11.0	12.1	12.0	12.7	8.8
OAc	1.99 s	2.07 s	2.06 s	1.97 s	-	2.10 s	19A,6β	-	0	0	0	1.2	0
	-	1.95 s	2.02 s	-	-	2.09 s	19A,10β	0	0	0	0	0	0.8
20-OMe	3.26 s	3.18 s	3.28 s	3.22 s	3.32 s	3.32 s	6β,6-OH[f]	-	-	-	1.9	0	-

[a]All at 300 MHz, except for **32** (500 MHz), in $CDCl_3$ solution. Chemical shifts (δ values) are reported with respect to the signal of residual $CHCl_3$ (δ 7.25).
[b]Overlapped signal.
[c]Collapsed into a singlet after addition of D_2O.
[d]*Exo* hydrogen with respect to ring B.
[e]*Endo* hydrogen with respect to ring B.
[f]Disappeared after addition of D_2O.

Compound **31**: colourless crystalline solid, mp 208-210 °C (EtOAc - *n*-hexane); $[\alpha]_D^{20}$ -34.4° (*c* 0.776, $CHCl_3$). IR (KBr) ν_{max} cm^{-1}: 3140, 3120, 1510, 875 (furan), 3040 (oxirane), 1745, 1260 (OAc), 1725 (ketone), 2940, 2860, 1375, 1160, 1100, 1030, 995, 920, 890, 800, 740, 680. ^{1}H NMR: see Table 5. ^{13}C NMR: see Table 3. EIMS *m/z* (rel. int.): 476 $[M]^+$ (0.5), 416 (0.5), 343 (0.6), 287 (3), 200 (3), 173 (4), 171 (4), 162 (5), 159 (5), 147 (7), 145 (5), 134 (8), 124 (16), 105 (9), 95 (23), 94 (37), 91 (19), 81 (14), 79 (15), 67 (11), 55 (8), 43 (100), 41 (15). (Anal. Found: C, 62.81; H, 6.82%. $C_{25}H_{32}O_9$ requires: C, 63.01; H, 6.77%).

Preparation of compounds **12** *and* **13** *starting from* **28** *and* **31**.

Treatment of **28** (100 mg, 0.230 mmol) or **31** (50 mg, 0.105 mmol) with Na_2CO_3 (50 mg and 25 mg, 0.471 mmol and 0.235 mmol, respectively) in MeOH (50 mL and 20 mL, respectively) solution as described above for **10** also yielded **12** and **13** (in 10:1 ratio, overall yield 93% and 91% from **28** or **31**, respectively).

Preparation of (12S,20R)-19-acetoxy-4α,18;15,16-diepoxy-6α-hydroxy-7-oxo-17β-neocleroda -13(16),14-diene-20,12-(20-O-methyl)acetal (**32**) *from compound* **28**.

To a solution of **28** (150 mg, 0.345 mmol) in anhydrous toluene (20 mL) was added DABCO (8 mg, 0.071 mmol) and the reaction mixture was heated at 120 °C for 6 h under Ar. Evaporation of the solvent and column chromatography of the residue (Si gel, EtOAc-petrol 3:2 as eluent) gave **32** (65 mg, 0.149 mmol, less polar compound, 43% yield) and starting material (**28**, 78 mg, 0.180 mmol, 52%). Compound **32** (colourless crystalline solid) had mp 192-194 °C (EtOAc - *n*-hexane); $[\alpha]_D^{20}$ -35.7° (*c* 0.611, $CHCl_3$). IR (KBr) ν_{max} cm^{-1}: 3440 (OH), 3140, 3120, 1610, 1550, 1505, 875 (furan), 3080 (oxirane), 1750, 1260, (OAc), 1730 (ketone), 2960, 2860, 1450, 1365, 1150, 1115, 1080, 1045, 1015, 1000, 980, 910, 810, 750. ^{1}H NMR: see Table 5. ^{13}C NMR: see Table 3. EIMS *m/z* (rel. int.): 434 $[M]^+$ (0.4), 403 $[M\text{-}OMe]^+$ (0.4), 374 $[M\text{-}AcOH]^+$ (2), 283 (3), 255 (5), 219 (5), 191 (6), 189 (7), 163 (21), 161 (18), 147 (18), 125 (15), 121 (15), 105 (16), 95 (26), 94 (100), 91 (21), 81 (25), 67 (17), 55 (26), 43 (82). (Anal. Found: C, 63.63; H, 7.01%. $C_{23}H_{30}O_8$ requires: C, 63.58; H, 6.96%).

Treatment of picropolin (**7**) *and 6-O-acetylpicropolin* (**9**) *with 1,4-diazabicyclo[2.2.2]octane.*

Treatment of compound **7** and **9** with DABCO in the same conditions as those reported above for **28** was unsuccessful and starting materials were quantitatively recovered.

Preparation of teuvincentin C (**2**) *starting from 6-O-acetylisoeriocephalin* (**5**).

A solution of **5** (30 mg, 0.059 mmol)[14] and DABCO (5 mg, 0.044 mmol) in anhydrous toluene (30 mL) was heated at 120 °C for 7 h under Ar. Evaporation of the solvent and column chromatography of the residue (Si gel, EtOAc-petrol 7:3 as eluent) gave **2** (23 mg, 0.045 mmol, less polar constituent, 76% yield) and starting material (**5**, 4 mg, 0.008 mmol, 13%). Compound **2** had mp 221-223 °C (EtOAc); $[\alpha]_D^{20}$ -8.3° (*c* 0.361, $CHCl_3$) and IR, ^{1}H NMR and MS identical with those of teuvincentin C [12](lit. mp 220-225 °C; $[\alpha]_D^{22}$ -8.1°, *c* 0.246, $CHCl_3$). Comparison (mixed mp, TLC) with an authentic sample confirmed the identity.

Treatment of **27** *with sodium carbonate: derivatives* **33** *and* **34**.

To a solution of **27** (200 mg, 0.460 mmol) in MeOH (20 mL) was added Na_2CO_3 (200 mg, 1.886 mmol) and the reaction mixture was stirred at room temperature for 4 h. Work-up in the usual manner gave 153 mg (0.390 mmol, 84% yield) of a mixture of the tautomers **33** (ketol form) and **34** (hemiacetal form) in 1.3:1 ratio, as was established from the ^{1}H NMR spectrum (signals for the C-19 methylene protons in **33**: δ 3.75 and 4.56, both d, J_{gem} 11.0 Hz; for **34**: δ 4.14 and 4.44, both d, J_{gem} 7.4 Hz). Attempts at isolating these compounds by chromatography or by crystallisation were unsuccessful.

Sodium borohydride reduction of the tautomeric mixture (**33** *and* **34**) *to give (12S,20S)-4α,18;15,16-diepoxy-6α,7α-19-trihydroxy-neocleroda-13(16),14-diene-20,12-(20-O-methyl) acetal* (**35**).

A solution of the mixture **33** and **34** (150 mg, 0.382 mmol) in MeOH (15 mL) was treated with $NaBH_4$ (80 mg, 2.144 mmol) at room temperature for 45 min. Then, the reaction mixture was diluted with H_2O (50 mL) and extracted with EtOAc (3 x 50 mL). Work-up as usual gave **35** as the sole reduction product (130 mg, 0.330 mmol, 86% yield): mp 75-85 °C, amorphous white solid; $[\alpha]_D^{18}$ +44.3° (*c* 0.316, $CHCl_3$). IR (KBr) ν_{max} cm^{-1}: 3450 (OH), 3140, 1505, 875 (furan), 2940, 2880, 1450, 1160, 1100, 1070, 1025, 1000, 980, 920, 840, 800. ^1H NMR: see Table 5. ^{13}C NMR: see Table 3. EIMS *m/z* (rel. int.): $[M]^+$ absent, 344 $[M-H_2O-MeOH]^+$ (3.5), 314 (4), 245 (10), 203 (14), 192 (18), 174 (17), 163 (100), 159 (36), 147 (35), 145 (29), 135 (42), 121 (57), 117 (31), 105 (33), 95 (71), 94 (37), 91 (77), 79 (73), 67 (47), 55 (58), 41 (76). (Anal. Found: C, 63.64; H, 7.55%. $C_{21}H_{30}O_7$ requires: C, 63.94; H, 7.66%).

Acetic anhydride-pyridine treatment of the tautomeric mixture (**33** *and* **34**) *to give* **30**, *(12S,20S)-6α,7β-diacetoxy-4α,18;7α,19;15,16-triepoxy-neocleroda-13(16),14-diene-20,12-(20-O-methyl)acetal* (**36**) *and the tautomers* **37** *and* **38**.

Ac_2O-pyridine (4 mL, 1:1) treatment of the mixture **33** and **34** (153 mg, 0.390 mmol) for 10 days at room temperature and work-up in the usual manner gave a residue, from which the derivatives **36** (30 mg, 0.063 mmol, 16% yield), **30** (see above, 86 mg, 0.180 mmol, 46%) and the mixture **37** and **38** (55 mg, 0.126 mmol, 32%) were successively eluted from a chromatographic column (Si gel, EtOAc-petrol 2:1 as eluent).

Compound **36**: amorphous white solid, mp 95-105 °C; $[\alpha]_D^{19}$ -52.4° (*c* 0.225, $CHCl_3$). IR (KBr) ν_{max} cm^{-1}: 3140, 1600, 1500, 880 (furan), 1745, 1250 (OAc), 2950, 1450, 1370, 1100, 1060, 1030, 980, 960, 940, 790, 740. ^1H NMR: see Table 5. ^{13}C NMR: see Table 3. EIMS *m/z* (rel. int.): $[M]^+$ absent, 416 $[M-AcOH]^+$ (2), 402 (5), 314 (4), 313 (3), 193 (5), 175 (9), 163 (20), 161 (12), 145 (16), 121 (17), 105 (15), 94 (90), 91 (10), 81 (30), 55 (13), 43 (100), 41 (12). (Anal. Found: C, 62.83; H, 6.78%. $C_{25}H_{32}O_9$ requires: C, 63.01; H, 6.77%).

Tautomers **37** *and* **38**.

From the mixture of these tautomers the hemiacetal form (**37**) crystallised slowly from EtOAc - *n*-hexane: mp 145-147 °C. IR (KBr) ν_{max} cm^{-1}: 3400 (OH), 3150, 3130, 1505, 875 (furan), 1735, 1250 (OAc), 2960, 1440, 1370, 1300, 1160, 1110, 1100, 1070, 1030, 1020, 1010, 980, 975, 960, 920, 910, 890, 855, 810, 690. EIMS *m/z* (rel. int.): 434 $[M]^+$ (1.2), 402 $[M-MeOH]^+$ (0.7), 372 (1.5), 342 (2), 312 (3), 300 (4), 255 (3), 245 (12), 163 (29), 147 (13), 145 (14), 121 (15), 105 (14), 94 (51), 91 (30), 81 (38), 55 (22), 43 (100). (Anal. Found: C, 63.77; H, 7.10%. $C_{23}H_{30}O_8$ requires: C, 63.58; H, 6.96%). Compound **37** showed mutarrotation: $[\alpha]_D^{19}$ -0.8° (after 1 min), +7.8° (3 min), +22.1° (15 min), +22.1° (1 h)(*c* 0.515, $CHCl_3$). The ^1H NMR spectrum of **37** revealed that it was in equilibrium with the ketol form (**38**) in 1:1.3 ratio ($CDCl_3$ or C_6D_6 solution, at 20 °C). This ratio was modified by the temperature (1:1.3 at 20 °C, 1:1.5 at 35 °C, 1:1.6 at 45 °C) and the open form was always the main tautomer at those temperatures. Some significant ^1H NMR spectral data for the mixture **37** and **38** are the following (500 MHz, $CDCl_3$): **37** δ 5.31 (1H, br s, H-6β), 1.13 (3H, d, *J*

6.9 Hz, Me-17), 2.87 (1H, d, *J* 4.6, H_B-18), 4.84 (1H, s, H-20), 3.32 (3H, s, 20-OMe); **38** δ 5.13 (1H, br s, H-6β), 1.11 (3H, d, *J* 6.6, Me-17), 2.96 (1H, dd, *J* 3.6, 2.6, H_B-18), 4.55 (1H, s, H-20), 3.27 (3H, s, 20-OMe). ^{1}H NMR (500 MHz, C_6D_6): **37** δ 5.56 (1H, br s, H-6β), 1.41 (3H, d, *J* 7.1, Me-17), 2.67 (1H, d, *J* 4.7, H_B-18), 4.85 (1H, s, H-20), 3.10 (3H, s, 20-OMe); **38** δ 5.08 (1H, br s, H-6β), 1.13 (3H, d, *J* 6.8, Me-17), 2.86 (1H, dd, *J* 3.5, 2.3, H_B-18), 4.70 (1H, s, H-20), 3.08 (3H, s, 20-OMe).

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